DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

108TH MEETING

Friday, March 5, 2004

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Washington, D.C. 20003-2802
(202) 546-6666

P A R T I C I P A N T S

Jayne S. Weiss, M.D., Chairperson
Sara M. Thornton, Panel Executive Secretary

VOTING MEMBERS:

Arthur Bradley, Ph.D.
Michael R. Grimmett, M.D.
Allen C. Ho, M.D.
William D. Mathers, M.D.
Timothy T. McMahon, O.D.

INDUSTRY REPRESENTATIVE:

Ronald E. McCarley

CONSULTANTS:

Neil M. Bressler, M.D.
Jeremiah Brown, Jr., M.D.
Alexander J. Brucker, M.D.
Frederick J. Ferris, M.D.
Leo J. Maguire, M.D.
Janine A. Smith, M.D.
Walter J. Stark, M.D.

FDA PARTICIPANTS:

A. Ralph Rosenthal, M.D.
Malvina B. Eydelman, M.D.
Joseph N. Blustein, M.D.
Don Calogero, M.S.
Gene N. Hilmantel, O.D., M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WEISS: I would like to call this meeting of the Ophthalmic Devices Panel to order, and we will have introductory remarks from Sarah Thornton, the Executive Secretary of the Panel.

MS. THORNTON: Good morning. On behalf of the FDA, I would like to welcome you to the 108th meeting of the Ophthalmic Devices Panel.

Before we proceed with today's agenda, I have a few short announcements to make. I would like to remind everyone to sign in on the attendance sheets in the registration area, just outside the meeting room. All public handouts for today's meeting are available at the registration table. Messages for panel members and FDA participants, information or special needs should be directed through Ms. Annemarie Williams who is available in the registration area. The phone number for calls to the meeting area is 301-977-8900.

In consideration of the panel, the sponsor and the agency, we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room, and make your

calls outside the meeting area.

Lastly, will all meeting participants please speak clearly into the microphone and give your name so that the transcriber will have an accurate recording of your comments?

At this time I would like to extend a special welcome and introduce to the public, the panel and the FDA staff two new panel consultants who are with us at the table today for the first time.

On my right, Dr. Neil Bressler, Professor of Ophthalmology, with an international referral practice in the Retinal Vascular Center at the Wilmer Eye Institute of The Johns Hopkins University School of Medicine; and Dr. Jeremiah Brown, Jr., who is the director of Ophthalmology Research at the Walter Reed Army Institute of Research Laboratory at Brooks Air Force Base in San Antonio, in addition to maintaining a private retina practice with Ophthalmology Associates of San Antonio. Welcome, gentlemen.

Will the remaining panel members please introduce themselves, beginning with Rick McCarley?

MR. MCCARLEY: Good morning. My name is Rick McCarley. I am President of Ophtec and I am

the industry representative.

DR. BRUCKER: Alexander Brucker, Philadelphia, Pennsylvania, Professor of Ophthalmology at the University of Pennsylvania Scheie Eye Institute.

DR. FERRIS: Rick Ferris, I am the head of the Division of Epidemiology and Clinical Research at the National Eye Institute.

DR. BRADLEY: Arthur Bradley, Professor of Vision Science, Indiana University.

DR. MCMAHON: Tim McMahon, Professor of Ophthalmology, Department of Ophthalmology, University of Illinois in Chicago.

DR. WEISS: Jayne Weiss, Professor of Ophthalmology and Pathology, Kresge Eye Institute, Wayne State University, Detroit.

DR. GRIMMETT: Michael Grimmett, Bascom Palmer Eye Institute, University of Miami.

DR. MATHERS: Bill Mathers, Professor of Ophthalmology at Oregon Health Sciences University.

DR. HO: Good morning. Allen Ho, vitreoretinal surgeon, Wills Eye Hospital, Thomas Jefferson University.

DR. SMITH: Janine Smith, Deputy Clinical Director of the National Eye Institute.

DR. BRESSLER: Neil Bressler, already introduced.

DR. BROWN: Jeremiah Brown.

DR. STARK: Walter Stark, Professor of Ophthalmology, Wilmer Eye Institute, Baltimore, Maryland.

DR. MAGUIRE: Leo Maguire, Associate Professor, Mayo Clinic, Rochester, Minnesota.

DR. ROSENTHAL: Ralph Rosenthal, Division Director, Ophthalmic and ENT Devices.

MS. THORNTON: Thank you. I would like to note for the record that the panel consumer representative, Ms. Glenda Such, will not be in attendance today due to illness. Thank you, Jayne.

Conflict of Interest Statement

I would now like to read the conflict of interest statement for today's meeting. The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest

statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government.

Therefore, a waiver has been granted to Dr. Alexander Brucker for his interest in a firm at issue that could potentially be affected by the panel's recommendations. The waiver allows him to participate fully in today's deliberations. Copies of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Alexander Brucker, Neil Bressler, Frederick Ferris, Michael Grimmett, Allen Ho and Jayne Weiss. They reported interests in firms at issue but in matters not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you, Jayne.

DR. WEISS: Thank you. We are going to now have branch updates, Karen Warburton.

Branch Updates

MS. WARBURTON: Good morning. I would like to present one item of interest from our Branch. One of the device types that the VEDB reviews is the ophthalmic sponge, which is used during LASIK surgery. We have recently become aware of Medical Device Reports, or MDRs, that identified an association between ophthalmic sponges and diffuse lamellar keratitis. Testing of a sample of ophthalmic sponges from a lot associated with a cluster of DLK cases showed significantly higher levels of bacterial endotoxin

than a different lot. Additional MDRs have also reported an association between microkeratomes and DLK, although most of those reports did not implicate endotoxin per se.

Endotoxin has been shown to cause DLK in a rabbit model and there have been reports in the literature implicating endotoxin from sterilizer water reservoirs as a cause of DLK outbreaks. Additionally, a variety of other etiological factors have been suggested. However, endotoxin-contaminated ophthalmic sponges have not previously been identified as a possible cause of DLK. Endotoxin-contaminated water used during device manufacture is a potential source. Historically, FDA has not required that ophthalmic sponges or other devices used in LASIK surgery be pyrogen or endotoxin free, and they are typically not labeled as such, although many may, in fact, be endotoxin free.

Our Branch is working with other Center offices to make the ophthalmic community aware of this potential cause of DLK through letters to professional organizations and letters to the editor in journals which we anticipate will be published in the near future. We hope to encourage

reporting of DLK to FDA through MDR reporting, and to stimulate both user and FDA investigation into these outbreaks so that we can better understand the role that ophthalmic devices and endotoxin in particular play in DLK, and make changes in our product review policies if necessary. That concludes my update. Are there any questions?

DR. WEISS: Seeing no questions, thank you very much, Karen. We will now begin the open committee session with the general issues discussion and the FDA team presentation. Dr. Eydelman?

FDA Team Presentation

DR. EYDELMAN: Good morning.

[Slide]

Today's discussion is centered around clear lens extraction for the correction of presbyopia. I want to thank Dr. Blustein, Don Calogero and Gene Hilmantel for organizing today's presentation and preparing all the materials.

[Slide]

Clear lens extraction--or CLE as we will be referring to it for the rest of the day--for the correction of presbyopia is an intraocular surgical procedure where non-cataractous lens is removed and

replaced with a multifocal intraocular lens, allowing for both distance and near vision. The sole purpose of this procedure is for refractive correction.

[Slide]

There are several points I wanted to make sure panel members are clear on. CLE is not currently approved in U.S. for any indication. It has been performed, as all of you know, as an off-label practice for several years but mainly in eyes with high refractive errors.

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There are currently no standards or guidances available for clear lens extraction with IOL implantation.

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There is currently only one multifocal IOL approved in U.S., but there are quite a few under investigation. Only two IOLs are approved for improving near vision acuity in presbyopic patients, and that is the AMO Array and the CMC Vision. Several different devices utilizing quite various approaches are under investigation. Again, there are no standards or guidances for devices solely intended for the correction of presbyopia.

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An estimated 1.5 billion people worldwide have presbyopia. Therefore, devices approved for the correction of presbyopia will have a very significant public health impact.

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The challenge that faces us today is in trying to design a study which will be least burdensome for establishing safety and efficacy of the device for the correction of presbyopia while making sure that the significance to public health impact due to improper trial design is considered.

[Slide]

We want to make sure that we address all the appropriate aspects of the appropriate study design. So, today we will ask for your consideration on the control population; inclusion/exclusion criteria; acceptable adverse event rates; sample size; study duration; variables to be investigated; efficacy endpoints and quality of life assessment.

[Slide]

The goal, of course, is designing an appropriate clinical trial for evaluation of clear lens extraction for the correction of presbyopia.

The first step in pursuing that goal was identification of all relevant adverse events and their anticipated time course. In order to address that, we did quite an extensive literature search which Dr. Blustein will summarize for you.

[Slide]

DR. BLUSTEIN: Initially we looked for studies that related specifically to clear lens extraction for presbyopia. There were very few articles that addressed this topic. There were two that we found, Dick and associates and Packer and associates, that dealt with clear lens extraction for presbyopia. Both studies were using the Array multifocal IOL.

[Slide]

Dick and associates--their study was a prospective study with 25 patients. They were bilateral CLE with MIOL. The average patient age was 51, with a range of 44-62. The preop spherical equivalent ranged from minus 25.5 to plus 5.75 diopters. Follow-up was at 6 months and the outcomes for efficacy were very good, 100 percent binocular uncorrected visual acuity of 20/30 and J4 or better. However, 48 percent of the patients complained of star bursts and 36 percent complained

of halos.

[Slide]

Packer and associates, in a retrospective study of 68 eyes and 36 patients--their study was not limited to just clear lens extraction but 34 percent of the eyes had received additional procedures for astigmatism. The average age was 58 years old and the range was from 45-81. Preop spherical equivalent ranged from minus 7.5 to plus 6.5 diopters. Follow-up was at 3 and 6 months. The outcomes--again, there was good efficacy with 94 percent binocular uncorrected visual acuity of 20/40 and J5 or better. Close to 6 percent had symptomatic posterior capsular opacities requiring YAG capsulotomies. There were no complication rates and there were no reports or assessment of visual symptoms.

[Slide]

Clear lens extraction with monofocal IOLs--because there was limited information for the multifocals we looked at what was done with correcting other refractive procedures with clear lens extraction so we looked at three areas for ametropia, hyperopia and myopia.

[Slide]

Vicary and associates, in a retrospective study of 138 cases with average patient age of close to 49 years of age, ranging from 22-69 years of age, with a range of preop spherical equivalent of minus 23.75 to plus 11.62 diopters, with an average follow-up time of 5 months, with a range of 2-26 months, reported on the following outcomes: They had uncorrected visual acuity at 3 months with 90 percent at 20/40 or better and close to 50 percent had 20/20 or better. Retinal detachment at 5 months, there was one case so that gave a rate of 0.7 percent. Uveitis, again one case with the same rate. Posterior capsular opacification requiring YAG capsulotomies was at 8 percent. Additional refractive surgeries were performed in 7 cases.

[Slide]

For clear lens extraction for hyperopia there were several studies that were performed in U.S., England, Belgium, India and Greece. They overall reported good efficacy in these studies. The sample sizes were relatively small, ranging from 18 to 50 eyes. Patient age ranges were from 19-86, and this is across all these studies. The preop spherical equivalent ranged from plus 2.75 to plus 13 diopters. The follow-up was anywhere from

1-60 months in these patients.

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The complications reported for the clear lens extraction for hyperopia collectively in these studies were that for posterior capsular opacification requiring YAG capsulotomy ranged from 5.6 percent to 54 percent in these studies. Posterior capsular tears at the time of surgery ranged from close to 3 percent to a little over 5 percent. Two cases required IOL exchange. Then, there were single case events reported of iris prolapse, iridodialysis, corneal burn and malignant glaucoma. The malignant glaucoma case occurred two years after implantation. Endothelial cell loss was reported for one study after 12 months at 7.38 percent.

[Slide]

Then we looked at clear lens extraction for high myopia. There are several reported studies with high efficacy. The problems with these studies is that there are short follow-up times that are associated with them and also exclusion of lost to follow-up on patients.

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Colin and associates had a 7-year

follow-up of their study of clear lens extraction for high myopia. There were 52 eyes in 30 patients. Preop spherical equivalent average was minus 16.9 diopters and the axial length in 64 percent was greater than 29 mm. Average patient age was 36, a little over 36 years of age, with a range of 22-51 years of age. They had performed laser pre-treatments on anyone who had suspicious lesions for future retinal detachments, treating lattice, retinal tears and retinal holes. The results of this study showed that close to 60 percent were within 1 diopter of emmetropia and approximately 85 percent were within 2 diopters of emmetropia.

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Colin and associates reported the retinal detachment rate at 4 years and then again at 7 years. At 4 years it was 2 percent and at 7 years it was 8.1 percent. This points out the importance that retinal detachments can occur later in the postop period.

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In this study 75 percent of the retinal detachment had YAG capsulotomies prior to the retinal detachments. One eye had YAG one year

before the retinal detachment and two eyes had YAG two years before the retinal detachment. In the four eyes that had retinal detachments the best corrective visual acuity ranged from 20/30 to 20/200 and the visual acuity in the fellow eye ranged from 20/30 to 20/100 in the untreated eye.

[Slide]

The slide on the right shows the posterior opacification with YAG capsulotomies. At 4 years it was approximately 37 percent and 61 percent after 7 years. So, again, this is to illustrate that complications of posterior opacification can occur beyond the follow-up time, short follow-up time. So, after 7 years there was a significant number that also had complications of opacification.

[Slide]

The mean time to YAG in this study was a little bit over 48 months, ranging from 9-75 months. Close to 37 percent within 4 years of clear lens extraction had significant posterior capsular opacification and 61 percent within the 7 years. The odds ratio of retinal detachment after clear lens extraction and YAG versus no YAG was 2.0. Other complications that were reported in

Colin's study were subfoveal choroidal neovascularization in one eye which occurred 9 months after surgery, and there was a decrease in best corrected visual acuity in that eye from 20/50 to 20/200.

[Slide]

Ripandelli and associates were reporting from the refractive surgeons studies. They were reporting from the retinal surgeons perspective. They reported on retinal detachment secondary to clear lens extraction for high myopia. they saw 53 eyes in their practice. The preop spherical equivalent average was minus 19.5 diopters, ranging from minus 14 to minus 29. Patient age was an average of 37.5, ranging from 25-58 years of age. This is in Italy, this practice. Laser pre-clear lens extraction was performed in close to 58 percent of these eyes. The time after clear lens extraction to the retinal detachment average was 2.25 years and ranged anywhere from 1 month to 4 years. YAG capsulotomies had been performed in a little bit over 25 percent of these patients. Then, macular involvement was in 100 percent of the eyes that had been operated on.

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Twelve eyes were lost to follow-up because they didn't come back for surgery even though that was recommended. For retinal detachment repair, 88 percent had the retina reattached; 41.5 percent had proliferative vitreoretinopathy; 34 percent had posterior retinal breaks. The results are that 22 percent had best corrected visual acuity of 20/60 or better. One patient had hand motion in one eye and 20/100 in the other. The pre-clear lens extraction visual acuity in this patient was 20/20 and 20/25.

[Slide]

O'Brien and associates reported that for clear lens extraction for high myopia the efficacy is certainly encouraging, that this seems to be very beneficial in terms of correcting the refractive error. However, the potential complications still outweigh the risks.

[Slide]

Literature review for clear lens extraction--there was only one study with long-term follow-up. That was the Colin study that followed for 7 years. The rates of retinal detachment continue to increase postop, 2 percent at 4 years and then 8 percent at 7 years. Lack of long-term

retinal detachment rates post clear lens extraction is a concern. So, we did a little literature search on retinal detachment rates post cataract extraction.

[Slide]

About 40 percent of all retinal detachments occur post cataract extraction. Patient-dependent risk factors include age, gender, refractive state, fellow eye, status of the posterior vitreous. Those are patient-dependent risk factors.

[Slide]

Surgeon-dependent risk factors include surgical technique, whether it is intracapsular or extracapsular, phacoemulsification and also incision size, capsulotomy and maintaining anterior chamber depth. Intraoperative complications are also risk factors--torn posterior capsule or vitreous loss.

[Slide]

Then, postoperative risk factors include trauma and YAG capsulotomy.

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Norregaard and associates had a population-based Danish study which looked at all

cataract inpatient surgeries done from 1985 to 1987 with 4-6 years follow-up and patient age of 50 or over. They used a reference group of a cohort that was age matched, gender matched and had no previous intraocular surgery.

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The 4-year retinal detachment risk after cataract surgery for various surgical techniques was shown to be 3.2 percent for extracapsular without IOL; 2.8 percent for intracapsular cataract extraction without IOL; and 0.93 percent for extracapsular without IOL. The reference group had retinal detachment rate of 0.21 percent.

[Slide]

The 4-year retinal detachment risk after extracapsular cataract extraction with IOL was stratified by age. There were increasing rates with decreasing age, 2.43 percent for the age group of 50-59 years of age; 60-69 years of age, 1.51 percent; 0.82 percent for 70-79 years of age; and 80 and above was 0.47.

[Slide]

This relative risk for retinal detachment stratified by age, with the reference group having no intraocular surgery, shows that there is a

significant relative risk in the younger age groups. In the 50-59 group, they are over 20 times more likely to have a retinal detachment having had surgery; for 60-69 they are 12.5 times more likely to have retinal detachment; 70-79, close to 7 times more likely; and even 80 and older still, close to 4 times more likely to have retinal detachment when no surgery was performed.

[Slide]

Javitt and associates, did a U.S. population-based study looking at all Medicare beneficiaries having cataract extraction in the year 1984, with a sample size of over 300,000 and they excluded the younger age Medicare beneficiaries and only included the 66 and older group. Extracapsular extraction was done in 60 percent of these patients; intracapsular was done in 31 percent; and phacoemulsification in 9 percent. They followed this in the database for rehospitalization for retinal detachments over 4 years.

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In their study, they showed that the risk factors were dependent on race, with whites being 1.7 times more likely to have a retinal detachment

than Blacks and with the various surgical techniques the intracap having the greatest risk and phacoemulsification the lowest. The younger age is also at greater risk for retinal detachments compared to the older, and we will go into that a little bit more.

[Slide]

For 4-year retinal detachment risk after cataract surgery stratified by age, they found 2.2 percent for 65-59 years of age patients; 1.3 percent for 70-79 year-old patients; 0.6 percent for 80-89; and 0.2 percent for 90 and above.

[Slide]

When you look at the relative risk, the 65-69 year age group were 18 times more likely to have retinal detachment than the no surgery group; 70-79 years old, close to 11 times more likely to have retinal detachment; 80-89, 5 times more likely; and 90 or above, 1.67 times more likely to have retinal detachment.

[Slide]

Javitt did another study. This was based on a 5 percent sample of Medicare beneficiaries. They looked at inpatient and outpatient surgeries between 1986 and 1987. The sample size was over

57,000, and they looked at 3-year follow-up for retinal detachment.

[Slide]

The cumulative 3-year retinal detachment rate was 0.81 percent, which was a rate similar to the previous inpatient study. Also, they showed that younger patients were more at risk than older patients.

[Slide]

This is from the 3-year retinal detachment risk after extracapsular cataract extraction, showing 0.95 percent for the 65-69 year-old group; 0.51 percent for the 70-79 year-olds; 0.24 percent for the 80-89 year-olds; and 0.08 percent for the 90 and above.

[Slide]

Looking at the slide on your right, summarizing the Danish study and the earlier Javitt study, they found one-year rates for retinal detachment with extracapsular with IOL and for the Danish study it was 0.42 percent and the 4-year rate was 3.2 percent for extracapsular without IOL and then 0.93 percent for extracapsular with IOL.

In the Javitt study the one-year rate for combining extracapsular cataract extraction whether

it was with or without IOL was 0.3 percent and for phacoemulsification it was 0.4 percent. The 4-year rate was 0.9 percent for extracapsular cataract extraction and 1.17 percent for phacoemulsification.

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The relative risk for retinal detachment at one year in the Danish study, extracapsular cataract extraction with IOL was 14 times more likely to have retinal detachment than no surgery. At 4 years, extracapsular cataract extraction with IOL was 26.67 times more likely to have retinal detachment than no surgery; and extracapsular cataract extraction with IOL was 7.75 times more likely.

In the U.S. study at one year extracapsular cataract extraction was 10 times to have a retinal detachment, and with phacoemulsification it was 13.3 times more likely to have a retinal detachment. At 4 years the relative risk for retinal detachment with extracapsular cataract extraction was 7.5 times and for phacoemulsification was 9.75 times.

[Slide]

Rowe and associates reported on cumulative

retinal detachment rates after extracapsular cataract extraction and phacoemulsification. It was a population-based study in Olmstead County, Minnesota. It was an incidence study. They looked at retinal detachment diagnosed between 1976 and 1995. The retinal detachment rates were adjusted for age and gender and they were compared with non-surgical retinal detachment rates.

[Slide]

The cumulative retinal detachment rates after extracapsular cataract extraction and phacoemulsification at 2 years was 0.36 percent compared to 0.034 percent with no surgery. At 5 years it was 0.77 percent compared to 0.13 percent with no surgery. At 10 years it was 1.29 percent compared to 0.25 percent with no surgery.

[Slide]

Looking at this as relative risk, at 2 years it is 10.59 times more likely to have a retinal detachment with cataract surgery; at 5 years it was 5.92 times more likely; and at 10 years it was 5.16.

[Slide]

DR. EYDELMAN: In light of the literature summary that you just heard, the first question we

would like you to consider is do you recommend a control population for studies of clear lens extraction for the correction of presbyopia, or do you believe that the study subject's own preoperative data is sufficient for comparison?

[Slide]

If you do recommend a control population, which one of the following do you believe to be appropriate? Is it historical control, active control or some other control? Active control would imply concurrent enrollment in a study of subjects with no previous ocular surgery. For historical control that you would obtain from the literature, there are several options, subjects' status post CLE for correction of presbyopia or those that have had a composite of all different refractive indications; subjects' status post cataract extraction or those that had no previous ocular surgery. Those are, obviously, all choices we would like you to consider.

[Slide]

Any time we define an appropriate study population for the investigation the real issue is identifying patients for whom risk/benefit assessment warrants enrollment in such a study.

[Slide]

Therefore, the question we ask you is should the clinical study inclusion/exclusion criteria limit subject enrollment based on the criteria listed below? If yes, we would like you to discuss the appropriate ranges of each limiting criteria for inclusion in the study.

[Slide]

Under (a) is refractive error and axial length, and we would like you to consider each one, the hyperopia and its associated refractive range; emmetropia; myopia with its range; (b) subject's age.

[Slide]

(c) Degree of accommodative loss, and in that discussion we would like you to consider based on what measurement you are making your recommendations; (d) preoperative endothelial cell count; and (e) any other factors, such as BCVA.

[Slide]

As you heard from Dr. Blustein, there are several numbers that are reported in the literature but all the literature essentially concurs that subjects with no surgery have much less chance than those that do undergo a lens extraction.

[Slide]

With that in mind, we would like you to consider what should be the primary safety endpoint for the study?

[Slide]

Another consensus from the literature is that the younger subjects do, indeed, have higher cumulative RD rates and that is basically due to the vitreoretinal interface characteristics and the fact that the risk continues to increase over time and these subjects have essentially a greater number of years left to life after the lens extraction.

[Slide]

So, is retinal detachment primary safety endpoint?

[Slide]

After clear lens extraction with MIOL subjects might experience visual symptoms requiring IOL exchange. Therefore, endothelial cell densities should be adequate to withstand additional surgery. From the literature review you have heard only one number, 7.38 percent endothelial cell loss at 12 months after CLE. However, these losses are really consistent with

operative losses themselves.

[Slide]

Several years ago Don Calogero, myself and Dr. Aresnoff, from Toronto, performed a meta-analysis of a literature review to try to determine what is the operative endothelial cell loss secondary to cataract surgery. There we determined that 8.9 percent endothelial cell loss is seen secondary to extracap and 7.4 secondary to phaco. These are losses that were secondary to operative loss itself, i.e., the range was 2-6 months.

[Slide]

There is no long-term data on endothelial cell loss after clear lens extraction. Furthermore, there is very limited data on long-term loss after cataract surgery. We all know from the last several panel meetings that Bourne et. al. reported 0.6 percent CLE loss for eyes without any surgery. However, I don't think all of you might be aware of the fact that Bourne has also performed a study showing that after cataract surgery itself there is a 2.5 percent cell loss that continues annually. Now, this was at 10-year follow-up of a rather small cohort, 64 eyes, and

surgeries were performed from '76 to '82, both extracap and intracap, and some of the subjects were left aphakic. So, the accuracy of that number with respect to modern surgery is questionable, but the fact that there is continuous loss secondary to cataract extraction itself seems to be implicit.

[Slide]

In light of that, is endothelial cell loss perhaps a primary safety endpoint, or if not a primary, should it be a safety endpoint?

[Slide]

Once you discuss what should be the primary safety endpoint, we would like you to concentrate on the acceptable adverse event rate associated with this safety endpoint.

[Slide]

The next question that we would like you to consider is sample size and follow-up appropriate for clear lens extraction studies. Not to give you a blank screen, we did several sample size assessments so you have something to work with.

The slide on the left summarizes statistics that we ran for the sample sizes that would be required for maximum allowable RD rate per

year. Here we assume a historical control rate of 0.01 percent annual RD. So, in the first column we have different study duration options, 1 year, 2 years, 3 years. Just to give you an example, if we assume that the maximum allowable RD rate per year should be 0.3 percent, a study design would require 321 subjects. That is how this table reads. If you have any questions later I can describe it further.

[Slide]

We also ran sample size statistics for endothelial cell loss. There are two tables, this and the next slide. This one is assuming a fixed historical rate of 0.6 percent annual cell loss. Again, in the first column you have one, two or 3 year study duration. Across, 1,000, 1,200, 1,400 and 1,500 are some of the cell densities that we assumed for you to choose from as the minimum cell density that you would like subjects to have at age 75. As a reference, down below, in the yellow, I put down that the normal ECD at age 75 is 2,400 with a standard deviation of 500. So, once again just to try to explain to you how this table works, if you say that you would like for a subject at age 75, after having clear lens extraction performed

somewhere in their 40s, to end up with 1,200 cells, for a one-year study that would require 319 subjects and for a three-year study only 26 subjects.

[Slide]

As I showed you before, this is the same table but now assuming active control, i.e., you would enroll patients who are not operated and you measure their cell loss. With the same examples, one year for 1,200 would be 638 and for three years it would be 48.

[Slide]

So, the question is in order to adequately determine the rates of all the adverse events and complications of concern, what do you feel is the appropriate sample size and follow-up period for a CLE study for the correction of presbyopia prior to the submission of the PMA?

[Slide]

I stress "prior" because the next question deals with post-market studies. To clarify, the post-market process can detect, identify and describe new or previously undetected medical device hazards. It also has the advantage of using real-world medical device experience to confirm the

safety profile of the device that was established in the pre-market submission and it could be a condition of approval.

[Slide]

In light of that, do you believe a post-market study is indicated? If so, what is the appropriate type of study, sample size and length of follow-up for such a study?

[Slide]

Acceptable adverse event rates for posterior chamber IOLs at one year following cataract extraction are in the FDA grid. The updated FDA adverse event rates are listed for you on the left, and I will spare you going through them. Are these rates applicable for correction of presbyopia in non-cataractous eyes for CLE at one year postop? Again, we are comparing one year to one year but adverse events that were historically acceptable after cataract surgery now to eyes which have not had cataracts.

[Slide]

Should the acceptable adverse event rates be adjusted for the study duration recommended? If yes, how? Furthermore, do additional adverse events need to be collected? If so, what should be

their acceptable rates?

[Slide]

FDA believes that all multifocal IOLs' safety and efficacy profiles will have to be established in a cataractous population prior to initiation of a clinical trial in a non-cataractous population. MIOL performance in a cataractous population will, therefore, be known for all tests and sub-studies outlined in ANSI draft standards for MIOLs.

[Slide]

On the slide on the left I summarized for you in the first column all the measurements that are recommended to be performed on all study populations. In the column on the right are those that are done in sub-studies. Just to clarify, it is best spectacle corrected visual acuity at distance; near visual acuity with distance correction; uncorrected visual acuity at distance; uncorrected visual acuity at near; pupil size; lens stability; and subject survey. The sub-studies are defocus curves; fundus visualization; far contrast sensitivity; and functional performance.

[Slide]

Which sub-studies do you recommend for

inclusion in the clear lens extraction protocol for evaluation of performance in this non-cataractous population? A) is functional performance and the functional performance study determines deficits in functional vision secondary to optical effects or multifocal IOLs. An example is a driving simulation study which was performed for MIOLs.

B) is contrast sensitivity and the current recommendation is for grading contrast sensitivity tests to assess threshold for spatial gradings.

C) is defocus curves and defocus evaluation comparing clinical performance to the theoretical lens design. What is done is that a subject's best spectacle corrected visual acuity at distance is obtained for the subject, and then the subject is defocused in 0.5 diopter steps to minus 5 diopters.

D) is fundus visualization and the current recommendation is for the investigators to rate the clarity of the retinal image through multifocal versus monofocal IOLs.

Then there is the endothelial cell evaluation and I think you all know about that by now, and any others that you might recommend.

[Slide]

The only current performance efficacy endpoint for aphakic posterior chamber IOLs, from the FDA grid once again, is post-operative BCVA of 20/40 or better in 92.5 percent of the subjects. Is this applicable to non-cataractous eyes undergoing CLE for the correction of presbyopia?

[Slide]

Question 7 B), are the predictability--75 percent of eyes with MRSE plus/minus 1 diopter and 50 percent with MRSE plus/minus 0.5 diopter and UCVA endpoint of 85 percent with 20/40 or better, outlined in FDA's draft guidance for refractive implants, applicable for this scenario?

[Slide]

Do we need to establish a performance efficacy endpoint for UCVA at near in this population of subjects who are undergoing surgery for the correction of presbyopia? If yes, what do you recommend?

[Slide]

What additional performance efficacy endpoints, if any, need to be set?

[Slide]

Something that you all need to consider is whether a general population of presbyopes without

cataracts will be tolerant of potential optical aberrations associated with MIOLs.

[Slide]

How do you recommend that we evaluate patient's quality of life issues?

[Slide]

There are several questionnaires which are validated and recommended in our ANSI standards, Javitt, Vitale, Schein and NEI refractive. If you can make a specific recommendation about the applicability of these questionnaires or combination of them, we would greatly appreciate it. This concludes our presentation.

DR. WEISS: Dr. Eydelman and Dr. Blustein, your presentation was absolutely superb and I hope the clarity of your questions can be met by the panel's answer to your questions.

DR. EYDELMAN: Thank you.

DR. WEISS: Thank you very much. We are now going to open the open public hearing session. Before we do, there is a statement that the FDA requires me to read. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at

the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a sponsor its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

We have two speakers today. I will ask Dr. Adrian Glasser, Associate Professor at the College of Optometry, University of Houston, to come forward for his presentation. I will inform members of the panel that there will be an opportunity to ask questions, both to the FDA team as well as the open public hearing presenters, at

the beginning of the panel deliberations.

Open Public Hearing

DR. GLASSER: Thank you. I would just like to start by saying thank you very much for the opportunity to present.

[Slide]

I am going to be talking on the topic of pseudophakic accommodation measurements. As mentioned, my name is Adrian Glasser. I am an Associate Professor at the College of Optometry at the University of Houston.

[Slide]

I am a scientist with research interest in accommodation and presbyopia. I have research funding and I serve as a consultant to several companies with interests in accommodation restoration concepts. I am here in my capacity as an interested scientist and as a consultant to industry.

My attendance at this meeting has been sponsored by a company with interest in accommodation restoration concepts. I am not talking about any specific devices so I have no proprietary interests in anything I will be presenting in this talk.

[Slide]

The purpose of my presentation is to attempt to open a healthy, constructive and informed dialogue between the FDA, researchers, clinicians and companies with interests in accommodation restoration concepts on the issues and challenges of pseudophakic accommodation measurement.

[Slide]

The presentation that I will make is primarily directed at accommodative IOLs rather than multifocal IOLs. Accommodative intraocular lenses are IOLs designed to provide uncorrected vision over a continuous range of distances without multifocality by producing an optical change in the power of the eye through movement or through change in shape of the optic. These are IOLs designed to provide dynamic accommodation. Demonstrated proof of efficacy is important for accommodative IOLs and, perhaps even more so, if they are to be used for the correction of presbyopia after clear lens extraction.

[Slide]

Pseudophakic accommodation measurement is important for patient informed consent, for patient

risk/benefit analysis, for clinical study design and testing, for selection of clinical control groups, for inclusion/exclusion criteria in clinical trials, and in patient populations and for product labeling following FDA approval.

[Slide]

I am going to ask more questions in this presentation than I have answers for, and here are some to start. What will the FDA consider as the gold standard for pseudophakic accommodation measurement? How will the FDA determine if the benefits of an accommodative IOL outweigh the risks of clear lens extraction? What kind of accommodation testing will the FDA require for accommodative IOL clinical study designs? Will these be subjective tests, objective tests or a combination of both? What tests or instrumentation should researchers and clinical investigators become familiar with for these clinical trials? And, what kind of instruments will the FDA consider as appropriate for objective accommodation measurement, refraction to measure an optical change in the eye versus, for example, A-scan biometry to measure movements of an optic in the eye?

[Slide]

I want to talk a little about subjective testing of accommodation. Distance corrected near visual acuity with subjective push-up test and negative lens-induced defocus have long been, and remain, clinical standards for accommodation testing. These and other subjective tests are easily implemented, are routinely used clinically. They could readily by used in clinical trials and they provide widely accepted indicators of functional near vision, both for patients as well as for clinicians. However, these tests are not quantitative measures of accommodative amplitude and they do not unequivocally demonstrate an accommodative change in optical power of the eye. What reliance will the FDA place on these and other subjective tests for future clinical trials of accommodative IOLs?

[Slide]

I want to talk a little about producing an accommodative response. To measure accommodative amplitude a full and maximum accommodative response must be elicited from the subject or patient. Accommodation can be stimulated with near or proximal targets by inducing blur such as by

presenting minus lenses to induce defocus on a distant letter chart, or with pilocarpine drops directly applied to the eye. Some individuals accommodate poorly in some conditions to pure blur fuse for example.

If no accommodation is recorded, it does not necessarily mean that the eye cannot accommodate. It may simply mean the subject has chosen not to accommodate. Pilocarpine drops on the eye can be used to stimulate an involuntary accommodative response. Will the FDA consider pharmacologically stimulated accommodation for determining efficacy of accommodative IOLs?

[Slide]

I would like to talk a little about objective measurement of accommodation. Clinical infrared autorefractors rely on analysis of reflected light signals and often fail or are inaccurate when light is reflected off high index IOL materials.

Instruments often used to measure accommodation objectively in research labs are no longer commercially available. New developing instruments are lacking validation, are not routinely available now, and their availability in

the future may be uncertain.

Standard clinical autorefractors, while tested and validated on phakic eyes, have not been tested and validated in pseudophakic eyes and may, in fact, not measure accurately or may not measure at all in pseudophakic eyes. Lower accommodative amplitudes expected of pseudophakic eyes will place higher demands on the resolution of these instruments.

[Slide]

Continuing with objective measurement of accommodation, there is considerable uncertainty as to the availability of instruments that are capable of objective pseudophakic accommodation measure.

What objective instruments will the FDA accept or mandate for future clinical trials of accommodative IOLs? Have these instruments been validation to accurately measure accommodation either in pseudophakic or, in fact, in phakic eyes? Will these instruments be able to reliably measure pseudophakic eyes, and will these instruments be generally available for placement at multiple clinical sites?

[Slide]

I would like to talk a little about

comparison of performance with the standard or monofocal IOL. Comparison with the standard non-accommodative, non-multifocal IOL using accepted subjective clinical tests, such as distance corrected near visual acuity, can provide an indication of whether an IOL provides functional near vision beyond that which would be provided by the standard IOL.

Will the FDA accept subjective comparisons of near visual performance with standard IOLs for clinical trials of accommodative IOLs? If so, what level of improvement over the performance of a standard IOL should be demonstrated? How many standard IOL control patients are required to demonstrate efficacy of an accommodative IOL?

[Slide]

Finally, I will end by asking a few general questions about what is required to establish efficacy. For accommodative IOLs is it more important to establish the existence of accommodation or to establish the amplitude of accommodation?

If distance corrected patients can read at near after implantation of an accommodative IOL, is this adequate to establish efficacy?

Many products are FDA approved without a fully elucidated mechanism of action because they work. Would this be adequate for accommodative IOLs?

How long a follow-up will be required to demonstrate longevity of efficacy of accommodative IOLs? And, will testing standards for FDA approval be different for accommodative IOLs versus for multifocal IOLs? Thank you very much.

DR. WEISS: Thank you, Dr. Glasser. If you would remain at the podium for a moment, are there any questions from the panel while Dr. Glasser is up at the podium? Dr. Bradley?

DR. BRADLEY: Thank you, Dr. Glasser for that presentation. I think you raise a very long and challenging list of questions for the FDA and it really would take too long to go through all of them, but just a general question, you ask whether pharmacologically induced accommodation would act as a substitute for, let's call it, voluntary accommodation. In your experience, do you have any reason to believe that it is an effective substitute, or do you think there may be, for example, a possibility that although one can induce accommodation pharmacologically the patient could

not activate their accommodative mechanism willfully? Is that a possibility? Or, should we be happy with pharmacologically induced accommodation?

DR. GLASSER: I wouldn't suggest that as a substitute. I don't think that it should be the sole means of identifying whether an accommodative IOL can produce an accommodative change. I do think that it is an important addition perhaps to the armament of tools that can be used to assess the accommodative ability of an IOL.

Let me just add to that by saying that it is well-known from the literature that myopes, for example, have lower stimulus response functions than emmetropes. So, there may well be some individuals in the patient populations who struggle to elicit an accommodative response even if active accommodation is truly there, and it might be important to understand whether the lens inside the eye is capable of accommodation. I think the pharmacological approach provides a useful tool in that regard.

DR. BRADLEY: Thank you.

DR. WEISS: Seeing no other questions from the panel, thank you very much, Dr. Glasser, for

your presentation. We are going to then have Dr. Lane.

DR. LANE: Thank you, Dr. Weiss and members of the panel for inviting me to share some comments with you today about intraocular lenses for presbyopia.

[Slide]

I am in private practice in the Twin Cities. I am a clinical professor at the University of Minnesota in ophthalmology and among a number of different hats that I wear, I am a clinical monitor for Alcon Surgical, for which I am a consultant, and I am here today representing them and they have paid my expenses to be here.

[Slide]

As a means of introduction, I would like to talk about presbyopia as not being a normal state and, as I take out my reading glasses to try and read some of my notes, that certainly becomes very evident. It is a progressive, degenerative loss of the ability to accommodate and it is really no different than an eye with any other refractive error in that there is no structural damage done but, clearly, it is not a normal eye.

The impact on the quality of life is

driving an increasing patient demand for spectacle- and contact lens-free vision. There are very high expectations of the generally younger patient population for this as is certainly evidenced by the popularity of corneal refractive surgery.

[Slide]

As I look at things, there are really two pathways in which I think the agency can proceed. One is with the practice of medicine, that is to say let the market forces play themselves out. The second is to recommend formal clinical trials.

[Slide]

With regard to the practice of medicine, the existing off-label practice medicine approach of refractive lens exchange--which I am using synonymously with clear lens extraction so it depends whether you are coming from a cataract point of view or you are coming from a refractive surgeon point of view--is accepted in the ophthalmic community and is continuing, and this is continuing without the approved surgical options to address safety and efficacy. As we have already heard, there have been no studies that have been done looking at this in any long-term prospective fashion, and despite inadequate information for

surgeon and patient informed consent.

[Slide]

Therefore, what is probably reasonable and prudent is a refractive lens exchange clinical trial. The development of a reasonable, adequate and well-controlled study focusing on safety and efficacy assessment that will allow for the appropriate informed consent is essential. Well, "reasonable" is certainly a very nebulous term but what we are really talking about here is being practical. What we are talking about is using the already established safety record of modern cataract surgery, and what we are talking about is encouraging the use of existing regulatory framework and guidance, wherever possible, from the already existing body of information that we have about cataract extraction and about refractive surgery. We believe the study should also address the functional outcomes which are so important to this group of patients and is really what is driving the entire procedure.

[Slide]

The parameters to measure are very well-known and I don't think we have to reinvent the wheel here. Existing regulatory guidance

already provides the sound basis for many study measurement parameters: distance, intermediate and near visual acuity and binocular defocus; stability of refraction; contrast sensitivity; pupil size, visual disturbances and adverse events; intraocular lens observations and position; and certainly quality of life.

[Slide]

As we look through the data, and we have also done a very thorough literature search similar to what was presented by Dr. Eydelman, we need to mitigate the perceived risks with known outcomes for modern cataract surgery. This would include things like endothelial cell loss. Certainly, the similarity, however, of this refractive posterior chamber lens procedure to modern cataract surgery eliminates, we feel, any need for ongoing endothelial cell count measurements. We have a body of evidence in terms of modern clinical cataract surgery done in a modern fashion.

But retinal detachment--again, the numbers, depending on where you look, vary all over the board. The numbers that we looked at are similar to those that were presented by Dr. Eydelman and show that anywhere from 0.0-0.9

percent incidence of retinal detachment with modern phacoemulsification techniques in the post-1980 era. This was modern cataract literature that was surveyed for retinal detachment risk factors.

[Slide]

The risk factors that we identified that we believe should be proposed as potential exclusion criteria are similar to those that were discussed by Dr. Eydelman. We too found that age is a risk factor, especially less than 40; that high myopia is a risk factor, especially greater than 8 diopters; that axial length is a risk factor, especially greater than 25 mm; and that any history of peripheral retinal disease is a risk factor.

Certainly, there are surgically-related risk factors. Posterior capsule integrity is critical. There is loss of posterior capsule if there is vitreous loss. If there is a YAG laser capsulotomy the incidence, as has been seen, increases. However, with the use of modern lens removal techniques and new foldable intraocular lenses, I think that many of these risks can be minimized. Most of the studies Dr. Eydelman presented were from the early 1990s with larger

incisions, with PMA lenses, with different edge designs and with different surgical techniques. This is going to be a population of people that, by and large, will have larger pupils; will have softer lenses; will have many of the decrease in risk factors that we now see in the cataract population of patients that we are having to deal with. So, we should be able to perform safer surgery.

[Slide]

The results of our retinal detachment literature survey shows that the retinal detachment rate in lens removal patients, when applying the proposed exclusion criteria that were just mentioned on the slide, was no different than that occurring in the untreated population, which is between 0.0 and 0.1 percent with up to 8 years of follow-up.

[Slide]

With regard to control groups, and we certainly understand that this is a concern that has been voiced by the agency with regard to the study, efficacy goals really should be reasonably met without creating overly burdensome requirements. We feel we must reasonably weight

the potential issues for the patients against the value of the information to be gathered. Is it reasonable? Is it fair? Is it practical for a patient who comes in desiring refractive lens exchange to be randomized to no treatment? I think we must use the existing guidelines that we already have in place for refractive procedures, for laser procedures as we proceed and look at the choice of control groups.

[Slide]

In summary, we have a number of proposals that we would like the panel to consider. First, we would like to minimize the study size and the duration by employing the proposed exclusion criteria derived from the retinal detachment survey. Based on an incidence of retinal detachment of 1/1,000 using this exclusion criteria, a clinical study that would be powered to detect a difference would need to be an exceedingly large sample size.

We would recommend that we apply the study subject's own preoperative data to provide the best method of control This provides roughly the same statistical power as using a non-operated control. It is consistent with current guidance documents

and, importantly, it addresses the patient considerations discussed previously.

[Slide]

We would ask to utilize the preoperative endothelial cell minimum as an exclusion criteria based on the FDA phakic IOL requirement in the guidance that has already been given in that respect. Finally, we would ask to employ the appropriate quality of life assessments, as an example the RSVP survey.

[Slide]

In conclusion, I would like to take off my Alcon hat here for a moment and put on my hat as a teacher and as a practitioner and as a leader of a number of ophthalmic organizations. I recognize that there are a number of various interests at play here. From the patient's standpoint, we want to meet the demand of their increasing interest in being totally spectacle and contact lens free.

We want to provide safe and effective treatment that is based on real information and true informed consent. As a surgeon, I want to provide the opportunity to deliver a service desired by our patients which we can feel confident about with regard to safety and efficacy.

As the FDA, I think you need and want to fill a vacuum that presently exists and to set a threshold of safety which we can live by and industry, while certainly not in this for only altruistic reasons, does want to produce products that are safe and effective to fulfill patient needs.

Finally, one that is not listed is societal. Refractive lens exchange allows the potential for generations to come to reach Medicare age with their lenses already removed, saving government billions of dollars and, thus, becoming the ultimate cataract preventative.

[Laughter]

All joking aside, I do see a real opportunity here but unless reasonable and practical considerations are employed, this increasingly popular procedure will continue to be performed outside the scope of the best interests of the above parties. Thank you.

DR. WEISS: Thank you, Dr. Lane. Do we have any questions from the panel? Dr. Grimmett?

DR. GRIMMETT: Dr. Lane, thank you for your presentation. I have a question regarding slide 7. I did a literature review over the last

year or so when we discussed phakic IOLs and endothelial cell loss and the long-term endothelial cell loss rates we have been basing off old data from Bill Bourne regarding procedures that we really no longer perform. You indicated on your slide that we have known outcomes with modern cataract surgery for endothelial cell loss rates and I was wondering if you could direct me to the literature reference or data regarding those known outcomes.

DR. LANE: I am sorry, Mike, I misspoke. As you well know, there are no known--basically I am using the numbers that have been used, and have been used by the agency to go forward with a number of the other studies that have gone forward and approval processes for new intraocular foldable lenses, and so on, using those data. I guess from a historical perspective, if you will, the basis of the endothelial cell counts from studies that have been performed most recently with more modern intraocular lenses, foldable intraocular lenses, that have achieved approval by the agency seems to be sufficient to allow approval of those particular lenses. So, really I guess what I am referring to is data that has been presented from previous

applications, if you will, of foldable intraocular lenses and the endothelial cell counts coming from those and coming from oncoming studies that will be looking at some new foldable lenses coming down the line. So, from a literature standpoint in terms of going back and looking at the literature and is there something out there that you have missed, the answer is no.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Thank you for your presentation. I have a similar question regarding the rate of retinal detachment. It would seem that your slide suggesting that the rate of retinal detachment in a select group after cataract surgery is no greater than those that do not have cataract surgery. But we heard this morning of several very large studies indicating that the retinal detachment rate is considerably higher, and also is highest in the youngest population for which we seem to have the least amount of data. Could you explain this discrepancy?

DR. LANE: I really don't see that there is a discrepancy, Dr. Mathers, because the literature that was discussed this morning included the entire cohort. What we are doing is separating

out the high risk factors. We are separating out the patients with high axial lengths. We are separating out the patients with high degrees of myopia. We are separating out patients with known peripheral retinal disease. So, the numbers that were given that are higher are based on the entire cohort that would include those while this group includes only those that have those exclusion criteria.

DR. MATHERS: But do we have literature that shows what the detachment rate in the younger population with cataract surgery actually is?

DR. LANE: I don't know the answer to that, and I certainly don't think we know--I don't know the answer to that.

DR. WEISS: Just as a follow-up question to that, if we are going to be suggesting that they should be used in younger patients or used in higher myopes, what would you suggest then be used in those cases that we don't have the answer for adverse event follow-up in terms of duration as well as percentage?

DR. LANE: A very good question. I don't obviously have the answer to that either, but I think that in the same way in which Dr. Eydelman

suggested that the introduction of any presbyopic lens be performed in a cataract population first, the next logical step to me would be to perform it in a group that included certain exclusion criteria that we are talking about. If that trial proves to be successful, as it would have to be if it was going on to the next step, then the next step would be to try some of the higher risk population and perform adequate studies to be able to show that.

DR. WEISS: Just a follow-up question, if you were putting this study together what would you want in terms of range of refractive error? It sounds like you would be suggesting that the refractive errors that are most in demand to have this done, namely the very high myopes, be eliminated from an initial study and the younger patients be eliminated from an initial study. Or, am I misreading what you are saying?

DR. LANE: No, you are not misreading what I am saying. I think that, you know, based on the literature search that we did looking at the exclusion criteria that are present, that is the group of patients that I think should be targeted. While, yes, the high myopes would certainly benefit potentially from this kind of technology and may be

the ones who would really sort of gather at your doorstep to do this in greatest numbers, for the time being certainly all of the literature suggests that those patients are at higher risk. So, I think, again, that may be a study that needs to be done in a better fashion using more modern techniques but I think we have to get there probably in a step-wise fashion rather than trying to do it.

I wouldn't necessarily agree that the majority of patients who would want to have this are necessarily the high myopes. There is a whole group of presbyopic patients out there who would want to have this for presbyopic reasons. While that certainly is an important group, it is certainly not the only group and may not even be the largest group.

DR. WEISS: Dr. Stark, did you have a question?

DR. STARK: You did show a reference on slide 9, Solomon, indicating that the retinal detachment risk was 0.1 percent. It went by so fast I didn't get it--

DR. LANE: That is in the untreated population. That is very similar to the

information that Dr. Eydelman presented. It is essentially a control group, if you will.

DR. STARK: Oh, okay. Good.

DR. WEISS: Seeing no other questions from the panel, thank you very much, Dr. Lane, for your presentation. Dr. Randall Olson has a letter that Sally Thornton will be reading as part of the open public hearing presenters.

MS. THORNTON: This is a letter from Dr. Randall Olson, who is the John A. Moran Presidential Professor and Chair of the Department of Ophthalmology and Visual Scientists, and Director of the John A. Moray Eye Center at the University of Utah Health Science Center:

I would like to comment on the use of intraocular lenses for correction of presbyopia after clear lens extraction, a topic that is to e discussed by the Ophthalmic Devices Panel of the Medical Devices Advisory Committee on Friday, March 5, 2004. We have performed about 100 "clear" lensectomy procedures in presbyopes over the past two years. The term "clear" lensectomy is a misnomer for us. In our patient population, it is rare for a presbyopic patient not to have some level of lens opacification, even though it may not

be significantly decreasing their Snellen visual acuity. In a study, done by Waltz, Wallace in Ophthalmic Practice, 2001, of over 200 refractive lensectomy patients, the average age at surgery was 53 years, our average is even older. We feel that we are doing these patients a disservice to perform corneal surgery, such as LASIK, when cataract surgery due to further lens opacification may be just around the corner. The precision of the refractive component of cataract surgery drops precipitously for post corneal refractive patients, and it is precisely this group that demands refractive precision.

For the patient, clinical studies have shown a high rate of patient satisfaction with refractive lensectomy. They perceive being "spectacle free" as an improvement in their quality of life. With the present levels of refractive precision, the acceptance rate is as good as, or better than, LASIK.

The only concern for refractive lensectomy that could conceivably be greater than cataract complications is the possibility of an increased rate of retinal detachment following surgery in high myopes. The retinal detachment risk is not

germane for emmetropes or hyperopes. We have published several studies in this area, Powell, Olson Journal of Cataract and Refractive Surgery, 1995, Olsen and Olson in the Journal of Cataract and Refractive Surgery, 1995, and Olsen and Olson in the Journal of Cataract and Refractive Surgery, 2000, showing a decrease in the rate of retinal detachment as surgical techniques and equipment have improved. For high myopes, the risk probably can be reduced by careful prescreening and the use of a phaco technique that maintains the depth of the anterior chamber during surgery. It should also be noted that the lens is less dense and more easily removed in refractive lensectomy patients than cataract patients. This reduces surgical complications for this group.

In spite of the issue of retinal detachment in high myopes, which has been investigated in multiple studies, a prospective study of "clear" lensectomy does not seem warranted, in that our cataract database is already so large and so inclusive. In additional, to truly study "clear" lensectomy in presbyopic patients would be extremely difficult since few of these patients have clear lenses.

Signed, Randall J. Olson, M.D. Thank you.

DR. WEISS: Thank you, Sally. That will conclude the open public hearing session. We will break for 15 minutes before beginning the panel deliberations.

[Brief recess]

Panel Deliberations

DR. WEISS: We are now going to open the panel deliberations session and I will ask, Dr. Eydelman, if you could come to the podium and perhaps we could use the questions as a guidance. Actually, perhaps Dr. Blustein could come forward as well so that if there are any questions for the FDA from their panel presentation we could have the panel ask those at this time. Do any of the panel members have questions for FDA? Dr. Ho?

DR. HO: Malvina, just a question on the FDA grid for PC IOLs, what is that data derived from?

DR. EYDELMAN: One second and I will show you, I am just going to put the slide up.

[Slide]

This was a composite of all the PMA data that was performed. As you see, the total N was 5,906 eyes. This particular grid encompasses all

surgeries from '87 to '96.

DR. HO: So, it is a mixed bag with respect to the way the cataracts were removed I suspect.

DR. EYDELMAN: Correct. We actually looked at this specific question two days ago because we were considering it under ISO. We have unofficially re-looked at what these numbers would be if we just moved it forward.

MR. CALOGERO: At the last ISO meeting this week we looked at updating the grid and we did some early, preliminary work. Unfortunately, I don't have the grid values. They changed somewhat but what we did, we truncated off the oldest PMAs and now, if you look at the data from 1994 out to 2003, there are minor changes in these rates but the retinal detachment rate goes down somewhat.

DR. EYDELMAN: The only number that was significantly different was the CME. It went from 3 percent to 1.5 percent. But since that was unofficial, sort of our little draft, we didn't put that up. This is the official FDA grid that the companies have been comparing their IOLs to.

DR. HO: Thank you.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: A question in follow-up, Dr. Eydelman, did the hyphema rate go down?

DR. EYDELMAN: Slightly.

GRIMMETT: Slightly?

DR. EYDELMAN: Slightly. For the purposes of ISO, we were looking if it would change at all our sample size for determination and it didn't.

DR. GRIMMETT: That is surprising to me because, at least in my clinical practice, it is just not common to see hyphema after modern phaco surgery. So, I am just surprised by that.

DR. EYDELMAN: I think it was 1.5. I don't want to quote, I don't have the numbers but it was over 1 percent. Again, cumulative is defined as occurring any time between surgery to one year. It is just additive.

DR. WEISS: Mr. McCarley?

MR. MCCARLEY: Yes, Rick McCarley. I have three quick questions. Hopefully, they will have quick answers. Are we limiting the discussion today to multifocal lenses and accommodative IOLs or are we also talking about standard monofocal IOLs where you would use monovision, for instance? In other words, any IOL that is placed in the eye to correct the patient who can no longer

accommodate?

DR. EYDELMAN: The discussion was intended to be limited to the correction where the subjects have both distance and near VA for correction of presbyopia.

MR. MCCARLEY: So, not for monofocal IOLs?

DR. EYDELMAN: Well, it could include accommodative.

MR. MCCARLEY: That is not accommodative?

DR. EYDELMAN: Correct. It is for those IOLs that simultaneously provide distance and near VA corrections.

MR. MCCARLEY: Okay. The second question is what is the FDA's current labeling for, for instance, accommodative IOL or the multifocal IOL related to the age range that they suggest? In other words, my understanding is it used to be 60 years and older but that was changed later on to be adults not less than 18 or not less than 21. Is that correct?

DR. EYDELMAN: Currently all IOL sponsors may require an indication for the adult population, but that is for IOLs status post cataract extraction, correct.

MR. MCCARLEY: My final question is the

FDA knows that this clear lens extraction has been going on for a while and knows that it is increasing in popularity. Has the FDA, in the interest of public health, done anything to inform doctors or patients now, working with maybe the AAO or the SCRS, to let them know what we know now so that they will be better informed for what we know is going on? In fact, what do you have planned between now and when any study might be completed?

DR. EYDELMAN: Well, as I mentioned, it has only been done as off-label and, as such, it has been quite an issue. Off-label means we do not have an approved indication with safety and efficacy data that we can share.

MR. MCCARLEY: So, you recognize there is a potential public impact but the FDA doesn't feel they can do anything right now to notify the doctors or the patients?

DR. WEISS: Do you want to comment on that, Ralph?

DR. ROSENTHAL: We are a regulatory agency that regulates the medical device industry and it is not our responsibility to inform the public about issues regarding off-label use unless we feel there is a significant public health issue.

MR. MCCARLEY: I thought that was how Dr. Eydelman's presentation started off, that this is a significant, major public health issue.

DR. EYDELMAN: No, my presentation started off that if CLE for correction of presbyopia becomes widely used it can have a significant health impact. As an aside, I said that CLE has been performed as off-label use, mostly for high refractive errors. Those two are two distinct ideas.

DR. WEISS: I think also some companies would like to get this on-label so I don't believe it is just being driven by FDA. Dr. Mathers?

DR. MATHERS: Is there any data indicating that the movement of an accommodative IOL would have any bearing on, say, position of the vitreous space or affect retinal detachment, uveitis or endothelial cell loss? In other words, there appears to be no downside to an accommodative IOL that changes its position but there might be compared to another kind of straight IOL. Do you have any data on that?

DR. EYDELMAN: No, we don't. We only have one, as you know, IOL currently approved so we have very limited information on that issue.

DR. WEISS: Any other questions from the panel? Seeing no other questions, we can then address the first question that the FDA is asking.

1 A), do you recommend a control population for studies of clear lens extraction in the correction of presbyopia, or do you believe that the study subject's own preoperative data is sufficient for comparison?

This is basically going to be a yes or no, and I want to poll each of the panel members if they want a control population or is the study subject's own preoperative data sufficient? We will start with Dr. Maguire. Would you like a control population, Dr. Maguire, or is preoperative data from the patient enough?

DR. MAGUIRE: I am going to pass right now.

DR. WEISS: We have an abstention. Dr. Stark?

DR. STARK: Well, I think it would be difficult to randomize patients, if they wanted this procedure, to no treatment or treatment. So, I think we could get enough information on complications if we had adequate long-term follow-up. My primary concern would be the retinal

detachment rate even in young people who are not myopic. So, I think we could get this from historical control or age-matched populations. So, I don't think a randomized, controlled study is necessary in this.

DR. WEISS: I am just going to step back for this question, for part A), it is not actually the type of control population but whether or not you want a control population. From what I understand from what you are saying, you do want a control population but not something so onerous but, still, you would like a control population. Is that correct?

DR. STARK: Yes.

DR. WEISS: Dr. Brown?

DR. BROWN: Yes, I do feel strongly about that. I would like there to be a control population, particularly if we include high myopes in any of thee studies.

DR. WEISS: So, you would like a control population as well. Dr. McMahon?

DR. MCMAHON: A question--we are jumping right into controls but are we talking from a perspective of efficacy or safety, or both?

DR. EYDELMAN: We are talking with respect

to study design.

DR. BRUCKER: Can I raise a question?

DR. WEISS: Actually, what I would like to do is not have a discussion now but sort of get a feeling for where people are at. Then, once we get involved in the type of control population we will break it up into discussion.

DR. BRUCKER: Could I still ask the question because it is applicable to what you are asking.

DR. WEISS: Okay, Dr. Brucker.

DR. BRUCKER: Clear lens extraction is a surgical procedure--

DR. WEISS: Yes.

DR. BRUCKER: That surgical procedure can be done by any physician at any time, period.

DR. WEISS: A hundred percent correct.

DR. BRUCKER: The risks and complications that we are talking about have to do with clear lens extraction. It has nothing to do with the insertion of an IOL. So, the question that you are posing seems to be a question that can't be taken out of that context. The insertion of an intraocular lens is not assumed, from my understanding, to be the cause of the complication.

Therefore, the use of a surgical procedure called clear lens extraction should have nothing to do, in my opinion, with whether you put in monovision, presbyopic vision or anything else; it is clear lens extraction. Perhaps we should have a little bit of discussion about the issue of clear lens extraction before you start talking about intraocular lenses.

DR. WEISS: I think technically what you are saying from a purist standpoint is correct, however, when IOLs get evaluated they get evaluated in terms of hyphema and retinal detachment rate and, from what you are saying, they shouldn't be evaluated in that way either because the IOL is not causing the RD or the hyphema but, yet, it is included in the surgical procedure and when the patient is going in for that surgical procedure you can't separate out for them that, oh well, this is the part that caused it and this part didn't cause it.

So, for the purpose of this discussion, although your points are well taken and FDA can correct me, I think it doesn't really apply. We still have to put it all together because when a patient is looking at it, who is 45 years old, who

is a minus 15, whether they are getting the RD 7 years down the line from the IOL or they are getting it from the surgical procedure they are still going to end up with an RD and that is the information they need. Agency, would you agree?

DR. EYDELMAN: You are absolutely correct because we are talking about approval of a particular IOL for a specific indication and that indication would incorporate a clear lens extraction which would precede the implantation. So, it is looked at as a package deal.

DR. BRUCKER: Yes, but you presented Ripandelli's work and many of the eyes in Ripandelli's work didn't have IOLs. They had clear lens extraction and they had retinal detachments. It is the retinal detachment coming from the clear lens extraction that really is the subject of discussion.

DR. WEISS: Dr. Brucker, as I said, I think from a logical technology standpoint, you are right but it doesn't apply to what the agency wants at this point. Dr. Bressler?

DR. BRESSLER: I think you do need a control, and it will be more interesting discussing what that will be on the second round.

DR. WEISS: Dr. Smith?

DR. SMITH: I agree, you need a control both for safety and efficacy.

DR. WEISS: Dr. Ho?

DR. HO: The clinician scientist in me wants an active control, however, I recognize the difficulty of executing a trial in which someone is seeking a refractive procedure and would be randomized--

DR. WEISS: Just to reiterate, we don't have to commit--

DR. HO: I would be okay with historical age and refractive-matched controls.

DR. WEISS: All I want from anyone right at this moment is do you want a control or you don't want a control. I am going to keep it nice and simple. It won't stay simple for long so enjoy it while you have it. Dr. Mathers?

DR. MATHERS: By patients on control, are you supposing that you do the surgery in one eye and not on the other?

DR. WEISS: Well, any type of control you want. It is just question 1 (A, do you want a control or you don't want a control? You are going to tell us afterwards what sort of control you

want.

DR. MATHERS: I want a control.

DR. WEISS: You want a control. Dr. Grimmett?

DR. GRIMMETT: Yes.

DR. WEISS: Dr. Grimmett wants a control. Dr. McMahon?

DR. MCMAHON: Yes.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: I am not sure.

DR. WEISS: Another abstention. Dr. Ferris?

DR. FERRIS: We have to have some sort of comparison group so the answer of who wants some sort of comparison group is simple, so I want a comparison group.

DR. WEISS: Thank you. Dr. Brucker just nodded in the affirmative. Mr. McCarley, you can voice your opinion, of course.

MR. MCCARLEY: I was just thinking of the same patient control.

DR. WEISS: Okay, and Dr. Maguire, did you want to voice an opinion at this point?

DR. MAGUIRE: Well, yes, because we haven't really established what we are talking

about so I don't want to say no.

[Laughter]

DR. WEISS: I take that as a continuation of an abstention. I am hearing somewhat of a consensus on 1 A), that most of the panel would like to have a control population. So, now we get into 1 B), which is on the screen, what type of control population would you like. We have the historical and the active, or if you can come up with anything else. I don't believe the FDA was emphasizing doing a randomized study. I don't really think anyone is talking about that, but if that is what you want to do you can certainly suggest it. In the list of controls under historical under 1 B) there are subjects--well, you can read them yourself. There are four different types of historical controls. There is one type of active control, and then if there is anything else that you would like. Dr. Rosenthal?

DR. ROSENTHAL: The active control would be a group of patients who had no surgery. So, in fact--

DR. WEISS: It could be randomized.

DR. ROSENTHAL: --you could randomize or you could just collect a group of patients.

DR. WEISS: Then the randomization is actually another level of specificity. You could have an active control of another group of, let's say, age- and gender- matched subjects, and how you wanted to include them in the study, actually, the FDA has not even asked us. So, they haven't even asked us for that level of detail.

Let's start with Dr. Maguire, if you wanted to voice your opinion on this.

DR. MAGUIRE: Yes, I think active control subjects with no previous ocular surgery and not planning on having any either for presbyopia would be reasonable.

DR. STARK: Agreed.

DR. MAGUIRE: Because we have no information on retinal detachment surgery in young people, or certainly not adequate information, and we would like to have more information on endothelial cell loss based on Dr. Lane's answer to Dr. Grimmett's question, so absolutely.

DR. WEISS: So, you would like an active control of subjects with no previous ocular surgery. Dr. Stark agreed with that. Dr. Brown?

DR. BROWN: Yes, an active case control study that is matched on criteria that we would set

out in terms of refractive error and age, yes.

DR. WEISS: So, you would also like an active control. Dr. Bressler?

DR. BRESSLER: I would like to discuss for a minute a couple of considerations for why a randomized control might be beneficial for getting the answer and then we can get back to would those people actually enroll.

We may see some visual acuity loss in a few of these people that have this. In the few studies that were done, granted in the high myopes with clear lens extraction they did have one or two people that are 40 losing a line of vision by six months, for example, in their best corrected visual acuity. Now, that could be to the detriment of this if you didn't have a control group because you would say, well, they started at 20/16 and they dropped to 20/25, or something. However, it could be that your control group developed some cataract along the way. We are going to have 50 year-olds with presbyopic symptoms, or whatever, and they may drop to 20/25 just as often. So, you never would have known that you weren't harming their vision, for example, more than if you left it alone if you didn't have a control group for that.

In addition, if you are going to look at quality of life outcomes, for example, whatever answers or change in the quality of life you get in someone over time, you just won't know if that is just due to the person having the surgery done and being happy with their life or if it is due to other factors that you would only get from a control group.

So, I am all for an active control and I think it needs to be considered as actually a randomized trial to be able to answer the important safety issue, which will be visual acuity besides the retinal detachment, which is much rarer and you may not be able to detect those changes, and any quality of life studies that might be considered down the line.

DR. WEISS: I would ask you if this could not be a randomized study because it was deemed that it would be too burdensome or the study wouldn't be able to accrue the patients because of that criteria, would you still want an active control? Would that still be something that you would want?

DR. BRESSLER: If you couldn't have it, then yes, but you might not be able to answer these

questions if you see that the visual acuity has declined. So, I just don't want to have the industry paint themselves into a corner. That is the whole advantage of doing this ahead of time.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: Along the lines of what Dr. Bressler just mentioned, the panel certainly can consider whether they wanted two different controls for safety and efficacy outcomes. If that is the case, that just puts a little further question into question 1 B).

DR. BRESSLER: I am not separating it because safety assessment depends on what the efficacy is as well. You are willing to take big safety risks for one sort of efficacy and less safety risks for another.

DR. EYDELMAN: Right, but determination of safety and efficacy with an active control is going to require greatly different sample sizes. Just keep that in mind.

DR. WEISS: Dr. Smith?

DR. SMITH: I would prefer to have an active control while recognizing these concerns that several have voiced regarding the feasibility of doing such a study, and I am open to discussing

ways to do that other than randomization but I do believe in active controls. It is critical to obtaining safety data in this age group for which we do not have good data.

DR. WEISS: Just to remind panel members, we welcome dissent. We don't need unanimity on this. This is really to guide the agency as far as the panel's sentiments so we don't have to have a continual roll here if you want to go in another direction. Dr. Ho?

DR. HO: As I was saying before, as a scientist I think that I would love to have an active control. I think it would be very difficult to execute that study. I think Neil's concern and point is a good one, however, the duration of the study will likely not be long enough so that maybe those 1/40 patients that drop a line might not drop a line in the first few years.

DR. WEISS: Would you be able to get a little closer to the mike?

DR. HO: Sure. Therefore, I would be open to a historical control but it would have to be an age-matched and refractive error-matched control.

DR. WEISS: Would that be difficult to do, Dr. Eydelman? I just saw a change in your

expression, not for the positive.

DR. EYDELMAN: Well, that would imply that each sponsor, depending on the inclusion/exclusion criteria, would have to go through the literature and try to see if they can pull--most of the articles don't have raw data so you would have to try to identify articles that have exactly the same age criteria as you wish to enroll. It gets a little tricky. We have done it for glaucoma devices and the sponsors found it quite difficult.

DR. WEISS: Dr. Bressler?

DR. BRESSLER: I just wanted to add to Allen's comment that in the small series we had from Dick and colleagues, that was only a six-month follow-up and they had 3/50--and I know these are broad confidence intervals but that was six percent losing one line. So, you might get those answers even with just a year follow-up or safety beyond two years.

DR. WEISS: Dr. Ho?

DR. HO: That was also a group that was highly myopic that might be more susceptible than the general group you are speaking to here who would like to have presbyopic surgery.

DR. WEISS: So, Dr. Ho, you still would

prefer to have a historical?

DR. HO: If that data can be derived, yes, because I think consideration of an active control--although burdensome and I would love it but I think it would be difficult to execute that trial.

DR. WEISS: Would I be able to ask you to sort of isolate one of the four listed here as far as what type of historical control? No, I would not be able to? Okay, well, I can ask. Dr. Mathers?

DR. MATHERS: I don't think it would be that difficult to have an active control because you are not really doing too much for these people if they haven't had surgery. You are just following them and you are doing some tests on them. But I think that you would have to stratify them to answer some of the questions. You would have to stratify them by axial length, refractive error, endothelial count and age. If you did that, you could answer these questions and I do think it is extremely important to answer these questions. We are talking about really major health issues here that affect millions, if not billions, of people and, clearly, the private community or the

academic community have all completely failed to look at this fundamental issue and maybe we have an opportunity to help them. We haven't answered these questions yet. Obviously, the literature shows we have not.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: For effectiveness issues I would be in favor of an active control. Certainly for quality of life issues it would be very nice to compare patients who have not had surgery with time to see how their quality of life compares to those who have had the surgery.

Dr. Eydelman read my mind as far as separating safety and effectiveness. I could go with a historical control for safety issues, perhaps patients who have had cataract surgery with IOLs.

DR. WEISS: I have just been informed that, unlike many panel meetings, my opinion is actually wanted on this one even though I am chairing this. So, I think I would like an active control as well because of the frustration I think for a sponsor as well as the panel often when the PMA is presented and we don't have the information to assess--let's say, the risk or whatever--and the

best way to do that is to compare it to an active control. Although randomization would be wonderful, I think it would be too onerous on the sponsors so I wouldn't be supporting that. Dr. McMahon?

DR. MCMAHON: I have a few comments on this issue. I agree with Dr. Bressler that a randomized trial with an active randomized control group would be ideal, but I also agree with you that it would be a bit onerous to maintain an active control group for a period of three or four years. Keep in mind, this is equivalent to a refractive surgery population and keeping track of the patients is hard enough, let alone controls who might also be interested in this procedure. If you are going to hold them off for several years I think it would be very difficult to manage this.

With regard to active controls, I think there are other mechanisms that can be played and I think it can be done in a variety of interesting ways. For the less common but more devastating complications like retinal detachment I can see a design where you have a prospective case control kind of circumstance where you have a lot of active controls who are not interested in the procedure

and a lesser number of actually operated patients.

But for things like efficacy you are going to want more of a matched controlled set of patients in that circumstance. So, I think an active control group is the thing to do. I think randomization is likely not to be manageable but there are other options I think that can be looked at.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: Yes, I have several comments. I think taking Dr. Brucker's comment earlier to heart in that potentially the greatest risk here is the surgical procedure not the lens being inserted into the eye, one might not imagine dramatically different risks associated with different lenses. So, we may, therefore, be able to employ historical literature controls for risk, particularly in the age group that has already undergone this particular surgery, which is obviously the 50-plus age group and they have obviously been having surgery for cataracts. So, this may be effectively evaluated using historical controls in the older group. That is certainly not the case if the lenses are going to be inserted in younger eyes. I think in that case an active

control for risk is required.

Regarding controls for efficacy, clearly, if we are going to be reviewing novel multifocal or novel accommodative IOLs, I think efficacy will require an active control. So, again, I am sort of dividing it between safety and efficacy. I think efficacy will require active controls even in the older group but safety may not.

DR. WEISS: Dr. Ferris?

DR. FERRIS: Some people may be shocked to hear me say this. In fact, I am shocking myself to say this, but I agree with Malvina that we need to look at this separately for safety and efficacy and I am saying that in part not, as Allen says, because of what is scientifically best but what is reasonable to do. From my perspective the appropriate control group, particularly for these younger people that are considering to have this done for presbyopia, is the unoperated group. The choice is wearing glasses and the risk of wearing glasses is pretty low.

So, the underlying rates that have been presented today for retinal detachment and endothelial cell loss are probably the appropriate rates to look at. They are so low that if you

tried to figure out the sample size that would be necessary to have reasonable confidence intervals around those rates, it is sort of an impossible study. So, from one perspective I would think that you would take the point of view that for safety the rate is almost zero or very low. So, what you want to know is what is the rate if you do this procedure and I would bundle the whole procedure as you were mentioning, the surgery plus the lens, plus everything. So, from the safety side I think that is the way that I would do it so I am saying I guess historical controls.

Efficacy is a different issue I think because now you can have an appropriate sample size and, as Neil pointed out, whatever it was, 6 percent loss or 3 percent one line loss is what you would find if you just repeated the visual acuity the same day. There is a certain 5-letter change in our experience. So, usually I say results are always improved by omitting the control group. In this case they are worsened by omitting the control group. So, i would think from the company's point of view they probably want an active control group and that control group may be several things. One, as mentioned here, their preexisting state, which I

think is a very important control group and, secondly, maybe a comparable group, particularly if you are going to look at changes over time and quality of life. I also agree that doing a randomization trial is virtually impossible. On the other hand, uncontrolled confounding is going to be an impossible issue to deal with when you don't have a randomization comparison. So, it is sort of skewed either way.

DR. WEISS: I think both Dr. Bradley and yourself bring up a very good point. Just to sort of elucidate it a little bit further, if you are going to be doing a historical control for safety, could you just clarify which one of those groups you would both be using?

DR. FERRIS: From my view, it is the untreated group, and the only caveat there is this untreated group is potentially treated. As was pointed out in discussions, eventually a large proportion of these people are going to have cataract surgery in their lifetime. The other thing that we will bring up later but what I think is very important is it is not the four-year risk of retinal detachment, it is the 25-year risk of retinal detachment.

DR. WEISS: So, you would like a historical control of subjects with no previous ocular surgery for safety but for efficacy have an active control. Dr. Bradley?

DR. BRADLEY: I think my views on the safety control group would be, again, the untreated group.

DR. WEISS: Basically you are in agreement with Dr. Ferris.

DR. BRADLEY: Yes, the one qualifier is that there is a presumption that the literature provides adequate data to support a historical control, and my reading of the literature and the presentations today lead me to believe that within the cataract age group we have adequate data to have historical literature-based controls but we don't in the younger age group.

Again, the question is where is the cut-off and I think that is perhaps for the FDA to determine. Where does the literature adequately provide this control?

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: If you are choosing to talk about appropriate historical control being subjects with no previous ocular surgery, then we have

adequate data in the literature for all ages.

DR. WEISS: Dr. Ferris?

DR. FERRIS: Well, just one other comment. The one place where perhaps an active control group would be useful for evaluating complications might be in the high myopes. A side issue related to what was discussed earlier is that I actually think it might be a mistake not to include that group because whatever happens with this study, that group is going to be at excess risk of having this done because they have excess benefit of having this done.

DR. WEISS: So, basically a historical control of subjects in, let's say, your routine cataract if we are talking about doing a minus 3 presbyope where you don't really expect there to be much difference from people without previous ocular surgery, but if you are doing the high risk patients, let's say the minus 20 myope, in that case you might want an active control. If you were doing a minus 20 myope, then neither of you would like a historical control at that point and would have an active control.

DR. FERRIS: It is actually in the company's benefit. This is one of those places,

again, where you would like to have the control rate because it is going to make your treated rate look better because the control rate is actually going to be significant. Otherwise, I am assuming the control rate is close to zero.

DR. WEISS: It gets a little sticky from the agency's standpoint--and correct me if I am wrong--if we are speaking about a historical control of subjects, except if we get involved in certain refractive categories in which case now we want to go on active control. Is there any guidance you can give us on that? I guess we will get involved in that when we get to question number two. Dr. Brucker?

DR. BRUCKER: I think that we are making this very complicated and unnecessary.

DR. WEISS: Welcome to the panel, Dr. Brucker!

DR. BRUCKER: I have been here and I will tell you we are making it complicated and it need not be. It seems to me that, unlike some of the comments around the table, these are patients who will go elsewhere for refractive surgery. That is not the case. These are patients who are perhaps 45-55 years of age and, like myself, they are

starting to have to use glasses. It is a pain in the neck and it doesn't matter if they are minus 14 or plano like I am. The fact of the matter is that these are patients that could use glasses. There is no reason that this isn't a randomization trial. It will make things simpler for the sponsor. It will make things simpler for the patient. It will make things simpler for the FDA. It makes things simpler for everybody to get a group of patients randomized and some will wear glasses. Okay, they have done it. It is only for three more years. And, some are going to have surgery. I don't see what the big deal is. The end result is you are going to have an idea. These patients are not going to have scleral depressed peripheral examinations. You are not going to know if they have lattice. You are not going to know what is going on in the back of their eyes. All you need to do is take a look again at Ripandelli's paper. Sixty percent of those patients wound up having pre-treatment. It doesn't matter if they are pre-treated or not. It doesn't matter what their peripheral examinations are. Randomize the patients. Spread it out whether they are high myopes, plano emmetropes or hyperopes. Give them

all a chance to be in the study. Make the sample size large enough. Follow them for three years and you will have all of your answers and there weren't be any complications or problems--let's not say complications.

DR. WEISS: Mr. McCarley?

MR. MCCARLEY: I think a historical cataract group would be fine unless the National Eye Institute would be willing to fund and run a study because it is actually the procedure we are looking at, regardless of the intraocular lens.

DR. WEISS: I have a feeling that is not forthcoming. Now we are going to go back; now that we have heard everyone's opinions, some of our opinions may have changed. Dr. Bressler?

DR. BRESSLER: I just wanted to clarify, are we talking about active controls for safety or efficacy? We haven't gotten to the question of what is the safety that we are looking at. So, I know we are in a circle and jumping in. I never foresaw in suggesting active controls that you want to power a study to see if there is a difference in the retinal detachment rate. I mean, that is low in the non-high myope population and that would take 40,000 or more and it wouldn't be meaningful

that you reduced it from 0.01 to 0.05 or something like that in percentage.

So, for certain safety outcomes you may have to deal with historical controls and there is adequate information for some of those. But for other safety outcomes, for example changes in visual acuity, you may be able to do it with randomized controls so you don't have all the confounding bias. As Rick pointed out, it is true that we had 3/50 in our limited information here that lost one line by six months and that could be noise; it may not be noise. It may be the beginning of two-line loss or three-line loss. It was mainly in the hyperopes, not in the myopes in that small study. That is 50 people versus--you know, there are 60 million over the age of 65 that are obviously going to be presbyopic.

So, I think it is incumbent upon the safety, not the retinal detachment safety but some of the others, to be aware of what these are; get rid of the confounding bias and, although it may be hard and take a little further discussion to get a group who is willing to put this off for a few years until we know what the outcome is, there are enough presbyopes out there--it is not a rare

disease--that it may be possible. So, I just wanted to add that clarification that I think I agree with what most of the panel said but I am still believing we would need for some of the safety outcomes these controls.

DR. WEISS: I am going to have one comment from Dr. Maguire and then I am going to ask if the agency needs anything more from us on this question, just because we have eight of these to get through. Dr. Maguire?

DR. MAGUIRE: I have a question for the agency. Does FDA separate groups for presbyopic correction if it is reasonable to expect that one of those groups is more likely to have problems with safety and efficacy, specifically the high myope group? That would be a reason to separate them out. Is that correct?

DR. EYDELMAN: In any refractive indication we usually break it up into the ranges of refractive error. For example, for LASIK we broke it up to 7 and above 7, and emmetropia would probably be analyzed separately. So, yes, the data would come in and then we would ask for internal stratification of the data according to refractive indication.

DR. MAGUIRE: But you would still run the study as a whole? In other words, you wouldn't place more stringent control requirements on patients with high degrees of myopia than the people with the other indications that led Dr. Lane to say they shouldn't be included at all in our discussion here.

DR. EYDELMAN: Well, it is certainly up to the sponsor to design what kind of trial they want to do and what inclusion criteria they want to expand their design to. We would certainly take your recommendations from today and try to give guidance to the sponsor accordingly.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: I know what Dr. Maguire is getting at, and I think if there is a marked discrepancy between two populations in the study one would probably ask to look at both of them together and then separately.

DR. WEISS: Dr. Smith has a quick question.

DR. SMITH: I just wanted to clarify an issue. In the first question here we are talking about clear lens extraction in the correction of presbyopia.

DR. WEISS: Yes.

DR. SMITH: Some of those patients may be myopic, hyperopic. We are not talking about their lens extraction for the treatment of high myopia.

DR. WEISS: We have not gone to question two, that is right.

DR. SMITH: But this is clear lens extraction and the indication is presbyopia. So, that doesn't cover 25 year-olds who are minus 20.

DR. WEISS: You are a hundred percent right.

DR. SMITH: So, I think that myopes are complicating our discussion.

DR. WEISS: Well, you might have a 50 year-old who is minus 20 and presbyopic.

DR. SMITH: Right.

DR. WEISS: We are going to then narrow things down as we go on, hopefully, but right now, from what I understand, most of the panel wants controls. Most of the panel is talking about active controls. Some of the panel is talking about historical controls for safety and active controls for efficacy, and some of the panel is talking about randomization. I would sort of like to cut things off at this point because we have

eight questions and we have sort of gone over on this one. Does the agency need anything else from us on that particular question?

DR. EYDELMAN: No, thank you.

DR. WEISS: Fine.

DR. BRUCKER: Jayne--

DR. WEISS: Sorry--

DR. BRUCKER: No, no, can you answer a question about something. Can somebody just tell me in a sentence about the range of accommodation of these multifocal intraocular lenses?

DR. WEISS: It is not relevant to this question. We are going to get there but basically I want to go in order. I mean, I can tell you the crystal lens labeling I think was 1 diopter. Dr. Brucker, from the PMA that was presented to the panel for the crystal lens, which is the accommodatve IOL that has been FDA approved, the labeling gave approximately 1 diopter of accommodation, for your information.

So, question number two, should the clinical study inclusion/exclusion criteria limit subject enrollment based on the criteria listed below? So, now what we are going to do is try to address in a succinct fashion each of the criteria

listed and their ranges.

The first one is refractive error/axial length. What would be the range that you would want for hyperopia? Do you want to include emmetropia and what is the range for myopia? Why don't we start with emmetropia? Do you think that a clear lens extraction trial for the correction of presbyopia should include emmetropes? Dr. Brucker, why don't you start on your end? Should we be putting plano people in here who need 2 diopters for their reading? Should they have clear lens extraction?

DR. BRUCKER: Yes.

DR. WEISS: Yes. Dr. Ferris?

DR. FERRIS: I apologize for this but I think it is going to take forever if we go through all of these. I think that what ought to be included is what is likely to be included in practice. So, if people are going in practice to include myopia, it needs to be in there. If they are going to include hyperopia, it needs to be in there. Are there extreme levels where you would want to exclude them? Yes, and I think that is the grey zone and we have to talk about that.

DR. WEISS: Actually, I think your point

is well taken. When we are going around, I am going to change sort of the question to you. Why don't you give me the refractive range that you would like? You don't have to say from this range to this range; you can stop around emmetropia or low myopia or low amounts of hyperopia if you would like. Some might want it to be only on the whole range. One example would be from plus 10 to minus 20. Another example would be that you might think it would be indicated from plus 6 to plus 10 and from minus 6 to minus 20 and not have the low myopes, the low hyperopes and the emmetropes. We can go about it that way. I think that is sort of addressing what you are saying. I understand there is a grey zone but where would you put the limitations?

DR. FERRIS: Right, so "I'll see you and raise you one."

[Laughter]

I think that I would exclude extreme hyperopia and extreme myopia but I would leave the definitions of that probably to the company, but I would want to include certainly to minus 10 and probably to plus 5, and I would be flexible on more and less--well, I am not sure I would be too

flexible on less. Where I am going to raise one is I think for moderate myopia, let's say over minus 4, I would like to power the study high enough so that you could say something specifically about myopia separately from emmetropia and hyperopia.

DR. WEISS: Well, I am going to ask for either abstentions or numbers because I think what the FDA really wants from us is numbers. That is why they are coming to us. From what I understand, you are saying from minus 4 to minus 10 in terms of the myopic range.

DR. FERRIS: I would like to power it so I could look at least at that range separately, and I would include, and I think this is totally arbitrary, but plus 5 to minus 14.

DR. WEISS: So, you are saying plus 5 to minus 14 and you would be including emmetropes.

DR. FERRIS: Absolutely.

DR. WEISS: So, you would be including plus 1's and minus 1's in that.

DR. FERRIS: Well, this is all about presbyopia, isn't it? Ask Dr. Brucker whether he is happy with his presbyopia.

DR. WEISS: Dr. Brucker, we won't to ask if you are happy with your presbyopia, but plus 5

to minus 14--

DR. BRUCKER: I am not happy with my presbyopia--

DR. WEISS: Okay, it is an aside and it will be on transcript for evermore. But what are your numbers, again? Plus 5 to minus 14 including those with your refractive error?

DR. BRUCKER: Yes, I would just say that you might want to look statistically. I wouldn't hold it exactly to where that minus 14 is if the numbers are so small that it isn't worth it. You must be minus 12 or minus 15, somewhere in that range is okay because the numbers get so small that it doesn't matter anyway. In other words, I think a minus 20 myope should be excluded but whether it be minus 12 or minus 14 from the standpoint of the FDA or the sponsor really doesn't matter to me. Do you understand?

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: No, I don't because what we are talking about is inclusion criteria--

DR. BRUCKER: Correct.

DR. EYDELMAN: --we are not talking about determination of sample size. Right now we are just trying to figure out for whom the risk/benefit

is such that it warrants inclusion.

DR. BRUCKER: Make is simple, make it minus 14.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: You are not going to like me. It seems that you are asking us the wrong question, if you don't mind me asserting that. You are asking us to identify a refractive range and age range for which the risk/benefit is acceptable. It seems to me the question should be what is the risk/benefit that is acceptable and then we will determine the refractive range. We have not identified the risk/benefit that we find acceptable.

DR. EYDELMAN: Unfortunately, from the design of the study we will first have to decide who we study before we give you the answer.

DR. BRADLEY: Well, I think the presentation this morning was trying to educate us on the risks, in particular retinal detachment, associated with lens extraction. If we have a sense of what that risk is and we can say what is an acceptable risk--is it 1 percent? Is it 0.1 percent? Once we have that acceptable risk, then the data will tell you what the acceptable

refractive range is; what the acceptable age range is. For us to do that in our head and come up with an acceptable refractive range and acceptable age range, quite frankly, is impossible. Therefore, I abstain.

DR. WEISS: Okay, so we have an abstention. See, I do like you, Dr. Bradley. Dr. McMahon?

DR. MCMAHON: All presbyopia short of nanophthalmos, up to minus 10.

DR. WEISS: Can you repeat that? For hyperopia you don't want those who are nanophthalmic?

DR. MCMAHON: Correct.

DR. WEISS: That is good.

DR. MCMAHON: Basically, that is about plus 8.

DR. WEISS: So, you would extend the level of hyperopia to just short of someone who has something pathologic and is going to get a devastating complication. And for myopia?

DR. MCMAHON: Minus 10.

DR. WEISS: Minus 10, and you would also include emmetropes?

DR. MCMAHON: Yes.

DR. WEISS: Uncharacteristically, I will abstain. Dr. Grimmett?

DR. GRIMMETT: I am less concerned about the range of hyperopia, albeit from a cataract surgeon's perspective it is difficult. You don't have enough interior chamber depth to do the surgery in high hyperopes through the shallow ACs. But I am in agreement with Dr. McMahon's comment that short of nanophthalmos I am not really too concerned about the level of hyperopia.

Myopia, I am a little cautious here due to the fact that these are performed on younger age patients and we saw this morning that high myopes have an increasing rate of retinal detachment that looked almost like an exponential function the longer you followed them out. I am up to minus 8 on the myopia.

DR. WEISS: And you would also include emmetropes?

DR. GRIMMETT: True.

DR. WEISS: I would ask the panel one question, if you have someone who is, let's say, plano and they have a decent chance of having the glare and halos and they are going to achieve a J3 or J5 with the risk of lens extraction, do you want

to include emmetropes? I am going to continue along and I know you have a comment on that, Dr. Bressler, but we will start with Dr. Mathers and continue along. Dr. Mathers?

DR. MATHERS: Well, I think it is a real ethical question about what we are recommending because as a scientist and a physician I would really like to know this data but I am very concerned about the relative risk of doing these clear lens extractions on relatively young people, particularly in their 40s or maybe even younger. I think that is going to get more difficult in the hyperopic group that are going to be pushing to have their surgery earlier.

But because this is being done now, I think it is imperative that we really find out, and I think that actually it is worth the risk of having a couple of hundred people be in this group to get us information even if there is an ethical question. I think we will solve the larger ethical question. And, I think there will be people who are willing to undergo that risk, a few people, and it won't take that many. But I think that we should be careful about extending the age range down too far. I can't tell you exactly what this

is but I am sure that we need the information in the younger age group but I would just be cautious about extending it down so I would go for hyperopic patients fairly high up to about a minus 10, minus 12.

DR. ROSENTHAL: Could I just comment on something? DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: The patients can't be too young because they are going to have to have some accommodative loss, which is number C). So, I don't think a 20 year-old myope with minus 20 is going to fit into that inclusion criteria.

DR. MATHERS: But a 30 year-old with a plus 5 would be knocking on your door.

DR. WEISS: Not necessarily, and I think we are going to get to that because we have criteria for degree of accommodative loss. Your level for hyperopia was--a number?

DR. MATHERS: Seven.

DR. WEISS: Seven. Dr. Ho?

DR. HO: I think Dr. Smith addressed this issue earlier where things start to begin to get a little less than grey. But to answer this question, I think, first of all, the notion of

active and separate historical controls is appealing and is a little different than what I described earlier. I think with respect to a range of accommodative refractive error I would be comfortable with anything that is non-pathologic on the hyperopic side. I am a little more protective on the myopic side, for this study design that you are describing, to minus 6.

DR. WEISS: Give me a number for hyperopia, if you would.

DR. HO: Plus 8.

DR. WEISS: Dr. Smith?

DR. SMITH: Plus 8 to minus 10, including emmetropes.

DR. WEISS: Dr. Bressler?

DR. BRESSLER: I am going to give you a number but you may not like it. I agree that we need to find out what is going on in the majority of the population that this may be appealing to, and I would like to say there is good data on what the refractive errors are, for example, in the United States and I would go with 95 percent of what the refractive errors are out there and exclude the extremes on either end. We can look up that number. I don't have it with me but the 95

percent is the number I want to use and I don't know if it is minus 8, minus 5, minus 6.

Then, I would add to the FDA's advice that there be a corollary to whatever this number range becomes to add to it something that many have alluded to, and that is if there are pathologic features that are normally associated with those extremes. So, we have people who are minus 3 every now and then but, because of the way their cornea and lens are, they are actually myopic and you can see the myopic changes. The same is true with the hyperopes. So, as you have your inclusion criteria for this, add something that includes those sorts of pathologic appearances.

DR. WEISS: And I think that would address 2 E) on this list for are there any other criteria. Thank you. Dr. Brown?

DR. BROWN: My concern is that regardless of how restrictive we make the study, the procedure will be done on anyone essentially and that is my concern. So, I don't want to be too restrictive and I would go along with Neil's recommendation of a 95 percent interval in the population, and I also think it will provide important data. The rate may be lower than we are expecting in that minus 6 to

minus 10. So, I think that I would go that way and be more inclusive for this study.

DR. WEISS: Dr. Stark?

DR. STARK: It was interesting to me that Dr. Lane's presentation from the company would restrict it to low myopes and low hyperopes just for presbyopia, and it would exclude all the pathologic cases. That may get them through earlier or sooner with less complications. But once it is approved, then it is going to be promoted as lens removal or lens exchange. So, I think we should have the range that will show us what the moderately high hyperopes and myopes do and if there are any potential complications. For example, myopes have larger eyes. A 4 mm optic in that myopic eye, that larger eye, larger pupil sometimes, may cause significant problems with nighttime vision. So, I would say in the range of a minimum of plus 6 to 10-12.

But also, we need to correlate that with axial length. I think Neil addressed the issue. Some of these people have a very flat cornea but an extremely long eye and are lower myopes but, in fact, they may have a 28 mm axial length. So, we may want to tie into this refractive range a

certain axial length. Certainly, an axial length of less than 18 is a nanophthalmic eye and it would depend on the cornea what the refractive error was. An axial length greater than 28 mm or 29 mm is one that is subject to a lot more potential for problems. So, we need to put that in with the refractive error.

DR. WEISS: Dr. Eydelman actually has included that in this portion of the questions. So, as long as you are bringing it up, Dr. Stark, do you want to exclude patients with an axial length greater than 28 or 29 and less than 18?

DR. STARK: Well, I would tend to include them but you may find your analysis of retinal complications in the high myopic population is more related not exactly to what the preoperative myopia was but what the preoperative axial length was. That is the important information for them, and also in the controls we would have to do axial length measurements.

DR. WEISS: You want axial length to be known in addition to the level of myopia or hyperopia but you would not be excluding people on axial length by itself.

DR. STARK: Well, I certainly would

exclude the hyperopes less than 18.

DR. WEISS: So, less than 18 would be the exclusionary criteria.

DR. STARK: And maybe less than 20. But we would have to correlate that with the refraction.

DR. WEISS: Would you have an upper limit of axial length for the high myopes or not?

DR. STARK: Probably 28.

DR. WEISS: So, 18 to 28 would be the range that you would want to be including in the study. Dr. Maguire?

DR. MAGUIRE: I agree with everything that has been said from the standpoint that we know there is a slippery slope on increased complications when you get to the very high myopes and the very high hyperopes. I have the same distaste for the idea of operating on emmetropes to correct presbyopia given the obvious public health issues that are here. But, you know, we have crossed the Rubicon already so we have to do this.

I also have a question for FDA. It seemed to me that at the last ocular lens panel discussion we had for guidance in the past, we were informed that there were monofocal IOL studies for low

myopia going on already. Isn't that correct? Down to like minus 2 or something?

DR. ROSENTHAL: Phakic IOL.

DR. MAGUIRE: Oh, that as phakic IOLs. Still, a phakic IOL is down to minus 3. So, we have crossed the Rubicon. We just have to get the information so we can not be in the type of problem we are now where we don't have information and FDA can't say anything.

DR. WEISS: Dr. Ferris?

DR. FERRIS: I just want to make a quick comment, and I rarely disagree with Dr. Bressler but the thing I worry about here is that we are dancing around what I think is the crux of this issue and that is informed consent. I think that we all have different risk/benefit internal ratios and the Hamlets shouldn't tell the Admiral Farraguts what to do, but I worry that if there is a special group that is at extra risk of having this done and is at extra risk of having complications, we need to have something to tell them about that extra risk because they are going to be told about the extra benefits--

DR. WEISS: I mean, we can just sort of add that to e) here, that those people who are at

more risk, they should have a little more detailed informed consent.

DR. WILLIAMS:

DR. EYDELMAN: That would be routine under the IDE procedures.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: No, I don't think that is what Dr. Ferris is getting at. He was getting at to include people at the extremes so that you can provide--

DR. FERRIS: Yes, if you don't have them you can't tell them what their extra risk is, and if you tell them what the risk in the study is--here is this minus 15 and you tell them we did this study and there wasn't any problem, that may be the wrong thing to tell them. That is why I said you need to power it enough so that you have some reasonably high myopes because they are at extra risk. Unless you are going to say absolutely never are you going to do this in high myopes, and we already know that is stupid because it is happening right now.

DR. WEISS: Just to play devil's advocate, I would say why limit it to minus 14?

DR. FERRIS: I wouldn't limit it at all.

But probably the truth is--what Neil was getting at I think, once you get above minus 14, and I don't know where the number is, you are going to have so few of them that you are not going to be able to really give good risk estimates. You are just not going to have them.

DR. WEISS: We need to sort of end this portion of it because we are really taking too long. From what I have heard from panel members, the high amount of hyperopia that has been suggested is to go up to plus 8, and it sort of varied between plus 5 and plus 8 but everyone has had the same sentiment that we want to avoid any patients who might have any indication that they could have nanophthalmos.

There has been consensus essentially on doing the emmetropes, the low myopes and the low hyperopes. There has not been anyone who has been against that. Then, in terms of the higher level of myopia, it had been expressed between minus 6 and minus 14 by various members of the panel but now I am hearing, Dr. Ferris, that you might go even higher if those people could be recruited because even if they had a higher adverse reaction that is something you would want to get into the

literature.

DR. FERRIS: Sure, and if I was advising the company I would tell them don't put those minus 20s in here. So, I am advising the FDA that I would like to see all the data I can have but I can understand, if I was doing this study, I would like to say, you know, these people are at special risk and I am going to tell them they are at special risk and I don't even want to include them in the study.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: Yes, my point when I was cut off which you now have accepted, which I do not appreciate, is the fact that if you go from a minus 14 to a minus, let's say, 28 and let's say you have 2 patients in every half step category, you may wind up having 20 or 30 patients in this range of minus 14 to minus 28 and not be able to analyze them because they are spread out so thin and that is such a rare population of patients.

My inference to you was look at the general population--Neil was saying 95 percent--take a look at the general population. Don't get yourself screwed up by having one patient in each of these half diopter refractions and not

be able to analyze them. Power adequately so that you have all of the bases covered, but make sure that you don't get yourself tilted on this last five percent, as Neil was saying, so you that can't answer any questions. That was my inference.

DR. WEISS: In addition to what I was just mentioning in terms of the range, there were two members of the panel who would prefer to look at the 95 percent. Do you have any idea what we would be talking about with a 95 percent refractive range?

DR. EYDELMAN: It would be much lower. It is definitely under 7 because we looked at it--

DR. WEISS: Myopia?

DR. EYDELMAN: Myopia. I don't have the numbers in front of me but I would venture to say somewhere around 4 or 5 diopters. I mean, it is pretty low.

DR. WEISS: Then, Dr. Bressler, if it only went up to minus 4 or minus 5 would you change your mind on wanting 95 percent? Of course, many of the patients who are going to want this are those with higher amounts of myopia and we won't have the information, which is sort of what Dr. Ferris was alluding to.

DR. BRESSLER: Yes, a little bit but not completely to what Rick said. So, you know, maybe go to 97.5 percent. But I am concerned about having any studies done on minus 15 or minus 20 or minus 24 at this time even to get the information because I think I already know the information, that there is a much, much higher risk of retinal detachment that far outweighs any immediate benefit I can see in terms of their gaining no reading glasses for presbyopia. We are talking about presbyopia, not their refractive error for distance. So, I am not ready to open the flood gates to it. I want enough of the minus 4's, 5's, 6's, 7's, 8's because they will be different perhaps from the minus 2's.

DR. WEISS: We will have one comment from Dr. Ferris, and then we are just going to sort of briefly go through the axial length because I think this is just basically a personal viewpoint which you can agree to disagree in terms of whether you want to have the data to document the higher risk, or whether your concern is with the individual patient and you don't want them being the one to get the retinal detachment and prove what you suspect might be occurring in any case. Dr.

Ferris?

DR. FERRIS: Just a quick comment, and that is that although I understood this comment about staging this and we will do the safe ones first and then we will do the risky ones next, I think the reality is that we have one shot at this, that there is not going to be the second study and maybe you can do post-marketing studies but I would like to review the history of how effective those are. So, I think there is probably one shot at getting this information.

DR. WEISS: Dr. Stark had suggested an axial length range inclusion from approximately 18 or 20 to 28 or 29. Would anyone from the panel disagree with that?

DR. STARK: I would probably go to 20; 18 really--

DR. WEISS: Is pushing it. So, we will change that from 20 to 28, 29. Dr. Grimmett?

DR. GRIMMETT: What is the old rule, 3 diopters per millimeter, or something like that, different from 24 mm as average? I am a little worried about the upper range. Probably around 27 or so, which would be about minus 9 I guess if you use the average rule of thumb, and then I would

probably do the same on the plus side, something like that.

DR. WEISS: Is that enough information for the agency on that one?

DR. EYDELMAN: Yes, thank you.

DR. WEISS: We are running late already. It is early but we are running late. So, we are going to go to b) and see how quickly that goes. We are going to break for lunch in a little bit but we are going to delay that just a tad.

Patient age, does anyone from the panel want to suggest a range? By the way, we don't have to limit any of these criteria so you could say you don't want to limit patient age but these are things that, if you do want to limit them, what would you like the range to be? And, if you don't want to limit them, we will hear from you. I am not going to go around on this one. I am just going to ask someone from the panel to propose if they want to limit age, and if they do, what they want to limit it to. Dr. Ferris?

DR. FERRIS: For me, I would go to C). If we are talking about presbyopia I don't care how old they are.

DR. BRESSLER: I concur. I don't want age

discrimination. It really depends on how the person presents. You could have a 35 year-old who happens to have what we are thinking of as the 50 year-old eye.

DR. WEISS: So, would anyone from the panel disagree with that? Dr. Mathers?

DR. MATHERS: But I thought that the issue of changing the vitreous face and retinal detachment predisposition increases as you come into the younger age group. So, I think age, in and of itself, is a relevant factor and if we are not careful we are going to be operating on mid-30s and the retinal detachment rate may be much different than in the 50 or 60 year-old group.

DR. WEISS: And you might operate on a mid-30s and that might be the one with the minus 15 or minus 12 or minus 10.

DR. MATHERS: Right. So, I would be more in favor of limiting it to, say, 45; maybe 40 but not less than that.

DR. WEISS: Is there any disagreement with that? Does anyone have a problem with limiting? Would you want to suggest 40 or 45?

DR. MATHERS: Well, ethically? We might as well get the data; let's go to 40.

DR. WEISS: So, we have a suggestion of a lower age limit of 40. Does anyone disagree with that?

DR. MCMAHON: I do.

DR. WEISS: Dr. McMahon?

DR. MCMAHON: The median age of patients coming in with enough symptomatic complaints for presbyopic correction is 44 so I would set the limit at 45. That way you would have reasonable certainty the patient has presbyopic symptoms.

DR. WEISS: Does anyone have any strong feeling that it should be less than 45? Dr. Mathers?

DR. MATHERS: The hyperopic group is going to be extremely, say, attractive for this procedure and we are not going to know how they are going to do. They are going to want this at 40 and I think we should find out because we have a chance here to find out. If we don't go to 40 now we are not going to go.

DR. WEISS: Dr. McMahon, does that change your opinion or no?

DR. MCMAHON: Dr. Mathers has a very good point and I balance that median age for presbyopic symptoms keeping in mind that presbyopes, many of

which go around uncorrected if they are relatively low presbyopes, come in with their symptoms earlier. At the same time, you raise the issue with regard to vitreous face issues and so forth, so I would still argue for 45.

DR. WEISS: Do you need anything more? No? That is fine. Dare we go to degree of accommodative loss? I see glucose levels dropping as I bring that one up, and preoperative endothelial cell count, after the last two panel meetings, my glucose level with drop on that one too. So, it is 12:10. We are going to be back here in one hours. Dr. Ferris?

DR. FERRIS: I am curious. Are we not looking at degree of accommodative loss because we can't measure it?

DR. WEISS: No, no, no. That was just a slight bit of poor humor. I assume that is going to take us more than three minutes to get through, unless anyone has the answer. Seeing no answer, we will break for lunch.

[Whereupon, at 12:10 p.m., the proceedings were recessed for lunch, to resume at 1:10 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. WEISS: We are now going to continue with panel deliberations. We are going to be changing the format somewhat in terms of trying to pare things down to get through these questions at a more rapid pace. So, I am not going to be going around polling anyone anymore. We are just going to basically throw the question out. If someone has a relevant comment, and I emphasize relevant, then please address it. We will be getting basically to all of the important questions but it serves the agency's purposes much better if we discuss the issue at hand when the issue at hand is in front of us.

So, we are going to now go on to 2 c), degree of accommodative loss. Does anyone on the panel have a comment as to whether the clinical study inclusion/exclusion criteria should limit subject enrollment on degree of accommodative loss and, if you think it should limit it on degree of accommodative loss, based on what type of measurement of accommodative loss? Does anyone have a comment directed to this? Dr. Bradley?

DR. BRADLEY: It seems to me that if the device that is to be studied has the potential to

provide a large degree of either accommodation or what has been characterized as pseudo-accommodation, which means without actual power change effective near vision is provided, then I would think the inclusion criteria would stretch to earlier ages and higher levels of residual accommodation. If the device only has a very limited accommodative range or limited amount of pseudo-accommodation, it would seem reasonable to limit the device to those who have only small amounts of residual accommodation.

DR. WEISS: Was that a definite maybe?

DR. BRADLEY: It means you can't have a single answer for every product. I mean, one answer doesn't fit all. It depends on how effective the product is going to be. The idea is if you have a lens that can produce half a diopter of accommodation it doesn't make a lot of sense to remove natural lenses that have 2 diopters of residual accommodation and replace it with a half diopter accommodating lens. Whereas, if the new lens has 4 diopters of accommodation, it makes a lot of sense to take out the 2 diopter residual accommodative natural lens and replace it with an IOL that gives 4 diopters. Does that make sense?

DR. WEISS: Is that good enough for the agency? Do you need more discussion on that? Dr. Eydelman?

DR. EYDELMAN: Yes, multifocal IOLs don't particularly have an accommodative range; they have a near visual acuity correction in a certain percentage of patients. None of the standards or guidances particularly cull out the accommodative loss prior to MIOL enrollment because obviously, we are treating cataracts. So, that would not necessarily be applicable for MIOL replacement.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: Yes, that brings us to the pseudo-accommodation issue. I think it would seem reasonable to me for the sponsor to have to convince the FDA. If they want to expand the range of patients to include those with larger amounts of residual accommodation, they would have to present the FDA with some sort of argument that these patients would actually benefit by this new lens. Does that make sense? For example, if you have a patient with 2 diopters of residual accommodation, arguably they can focus at 50 cm perfectly well. It seems to me the sponsor would have to convince the FDA to include those patients by suggesting

that with the new lens they would be able to see at closer distances than 50 cm, more than they would with their original lens.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: The issue was brought up by Walter or Dr. Mathers. If you have a patient who is going to be in the younger age group and is a hyperope and they still have some accommodative power left, they may be able to see J1 at 14 in. That is wonderful. But if they have lost everything else they are going to be coming around and saying, "wait, I used to be able to see everything on the table in front of me. I couldn't see up close but I could see everything on the table," and now you have taken their lens out. So, the question that he is raising is if you don't have an accommodative range, it is fine, take the lens out; put an IOL in their eye and it is not a problem. But if a patient has 2 diopters of accommodation left in their eye and they are 38 years of age or 41 years of age, is it appropriate to sacrifice that accommodative power because you are going to give them 14 in of no glasses up front? It may not be. And, that needs to be considered in the indications, the labeling, etc.

There may not be enough risk/benefit; there may not be a ratio that is worthwhile. If you still have all that accommodation the risks aren't worth it. If you are 55 or 60 years of age and, sure, you can't see anything on the table in front of you, put the IOL in their eye.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Regardless of what the accommodation is at the time of surgery, in a fairly short period of time they are going to lose a lot of that accommodation anyway. It may be that the efficacy is actually going to be better in hyperopes who still have accommodative levels intact because their ciliary body still acts better than for someone who has lost it and it would be interesting to find that out. So, I don't think that we should limit the entrance criteria but we should put in a reasonable effort in measuring afterwards to find out how efficacious it is in which group and for how long.

DR. ROSENTHAL: Excuse me--

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: It is rather difficult. They are going to have near visual acuity that can be measured. They are going to require plus 2 to

read J1 or plus 1.5 to read J1. Maybe we should take it from that viewpoint rather than from accommodative loss. What should we be including in the study? Shall we allow the sponsor to operate and implant a lens in someone who can read J2 with a plus 0.50?

DR. WEISS: Dr. Ferris?

DR. FERRIS: Well, one might ask how dumb the company is going to be to include those patients because, at the end of the day, they are going to have a lot more risk with including them. So, surely you would want to include people who are having trouble if your outcome is going to be that you have to show improvement.

DR. ROSENTHAL: What is trouble?

DR. FERRIS: Well, I agree with what I think you were saying, that you would like to say that they can read at some level and the world is grey. My world is grey and you can pick the level but I would think that these are people that can't read J2. I don't care what you pick but you had better be able to show that you have at least done them a favor by doing this surgery which is surely putting them at risk.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I think this morning Dr. Mathers said that we only get one shot at this and we should have our age limit relatively low because of that. He picked 40. He picked that because he wants to get at a critical safety issue, which is retinal detachment in young patients. I think we should just leave the degree of accommodative loss alone and cast a wide net because one of the outcomes might be that people with relatively minimal loss have decreased quality of life after the lens and that is something we need to know, if that stratifies by age. So, I don't think there should be an exclusion criteria based on degree of accommodative loss.

DR. WEISS: I would voice the opposite opinion because this is for correction specifically of presbyopia. I think we get to a slipperier slope if we have no criteria for accommodative loss. I would like to see that someone, indeed, required a plus 1.50 for near or plus 2 for near. Otherwise, why is this lens being used for presbyopia? Dr. Maguire?

DR. MAGUIRE: I respect that outcome but I would also respectfully submit that you are thinking in terms of simple spherocylindrical

optics and a lot of these lenses that we are going to see are going to give people simultaneously good distance and near vision because they work on the concept of increasing depth of field, and any lens that gives you vision through increasing depth of field pays the price of optical degradation to do it. We know that already because of the subjective complaints of these people. They all complain of halos. We know the optics are not that good but they form a positive opinion despite that in about 92-95 percent of the patients. So, I think you just have to let that go. I think you have to go with the low age group and not bring accommodation into it because we are on a lot of different simultaneous slipper slopes that counteract. I think we get one shot and we have to look at that.

DR. WEISS: Any other opinions on this issue? Dr. Ferris, Dr. Bradley and then I am going to ask you if you have enough information on this. Dr. Ferris?

DR. FERRIS: I actually think we are going to have to get to this when we start talking about efficacy and how we are going to measure it. That is going to determine what level of accommodative loss or what reading level you have because if you

are at the ceiling you are never going to be able to show improvement, if you understand what I mean by that. So, some of these other things that are down the road may come back to this.

DR. WEISS: So, you would like to show some degree of accommodative loss preoperatively.

DR. FERRIS: If you are testing presbyopia I would like to show that you have done something about it, yes.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: It is worth reminding ourselves that presbyopia is really two different creatures. In some sense we stop presbyopia in young adulthood but we only turn up at the clinic when we can no longer read. Accommodation is declining throughout our life. In some ways this study will be self-selecting. I mean, patients who are manifesting problems with their presbyopia, and it may be that they are down to 2 diopters of accommodation; it may be that they are 1 diopter hyperope and they are down to 3 diopters of accommodation. So, that may vary. The actual amount of accommodation may vary at the time the patient presents with problems with presbyopia. So, in some ways you might must let the patient

self-select this. They are seeing their clinician because they have a problem with presbyopia. Maybe that is the patient base you should use.

DR. WEISS: It appears that we have no consensus on this one. Is that sufficient for the agency?

DR. EYDELMAN: I guess it will have to do.

DR. ROSENTHAL: Actually, we have a consensus--

DR. WEISS: We have a consensus of one. Dr. Rosenthal?

DR. ROSENTHAL: --that is that if they have to have reading glasses for what we would consider a reasonable amount of dioptric power and the lens can achieve a better dioptric power at near, then I think it is reasonable. But I don't want to give someone who has plus 2.5 to read The Wall Street Journal--you know, I think that is putting people maybe at undue risk but I think we have a sense where we can go with that.

DR. WEISS: Dr. Stark?

DR. STARK: Well, you need to leave a little of your accommodative power in reserve so I would say that the need for reading glasses or bifocals and no more than 3 diopters of

accommodative reserve, and it could be no more than 2 diopters or no more than 4, but if you say 4 diopters, then in general people can get by with that and read. So, they are not just doing clear lens extraction and then throwing in a bifocal with it; it is for presbyopia.

DR. WEISS: Dr. Mathers, and then I think we will be concluding this.

DR. MATHERS: This is very much a moving target. It is a dynamic process when you are talking about what someone's accommodation is in January, the same year in December it is going to be less. In two years, by the end of the study, in two or three years, it is definitely going to be less. So, I don't think it is critical how you get in because we are all going to be there anyway and we need to spread a broad net.

DR. WEISS: Well, at least in my opinion, I am in agreement with Walter and Ralph, that we should have some documentation of some degree of accommodative loss in terms of needing a bifocal or accommodative reserve so you have something to compare it to as far as the success of this procedure. But we have, obviously, a mixture of opinions up here. So, if that is fine with the

agency we can go on. Is that okay?

DR. EYDELMAN: I just wanted to say something about clarification regarding what Dr. Ferris said. Obviously, when you are discussing efficacy criteria you will have to take that into consideration but normally the way we do the studies, it is not each individual subject's improvement.

DR. WEISS: Dr. Ferris?

DR. FERRIS: If you enroll people who don't need anything to read J1 how are you going to show that this treatment was effective? You can't show improvement if you have no place to go. It would be incredibly dumb for a company to do that because they are going to have some proportion of patients who didn't improve. Well, they didn't improve because they couldn't improve. Maybe they did improve. Maybe they could read J0.5 but we don't even have that. So, it would be silly to put people into a trial if the outcome--for example in some trial if 3 lines visual gain, it would be dumb to put 20/20 people in because they are not going to get 3 lines visual gain no matter how good your treatment is, or let's say 20/15. That was my point about the ceiling, that usually your

eligibility criteria are such that if your outcome is a certain level of visual improvement and that is at least possible to attain, otherwise you have a bunch of people who are going to be negative even if you conceivably help them.

DR. EYDELMAN: So, if I can just paraphrase what you are saying, you recommended in lieu of degree of accommodative loss an appropriate inclusion/exclusion criteria is uncorrected near VA.

DR. FERRIS: Well, the reason I said outcome variable is that it depends on what outcome variable you are going to choose. That is going to drive the eligibility criteria. So, if you choose an outcome variable that says you improve by a certain amount of accommodative amplitude, maybe it is the accommodative amplitude that drives it. If it is that you can read at a certain level, like J1, then you probably want to have people that can't read J1 at the start.

DR. WEISS: Dr. Rosenthal, did you have a comment?

DR. ROSENTHAL: No.

DR. WEISS: No? Malvina, you are fine? Okay. So, we are going to go on to a less

controversial point, preoperative endothelial cell count. Any thoughts on preoperative endothelial cell count? Should that be inclusion/exclusion criteria? Dr. Mathers?

DR. MATHERS: I think it should be an exclusion criterion because we do not want to do 40 year-olds with an 1,800 cell count.

DR. WEISS: So, have an age-related minimum before you could enter the patient in this study. Am I paraphrasing your correctly? Dr. Grimmett?

DR. GRIMMETT: I would be in favor of just what we discussed at the last couple of meetings of having a sliding scale, similar to what the FDA proposed based on projections into the future so you would have enough cells when you are older. So, the younger you are, you need a higher cell count. So, I would be in favor of exactly the sliding scale that we did before.

DR. WEISS: I would add something to that. I don't believe the sliding scale could be the same as the one for phakic IOL because you have more trauma induced by the cataract surgery on top of the IOL implantation, I would think. Or not?

DR. EYDELMAN: Well, the sliding scale is

obviously going to depend on what your endpoints are, but I think you can discuss that in relationship--

DR. WEISS: Okay. So, I think there is some thought about having that as an inclusion criteria, with the FDA coming up with endothelial cell counts per age. Any other factors that should be inclusion or exclusion criteria? It was mentioned by Dr. Bressler before that patients with pathologic changes, that should be included as exclusion criteria as far as hyperopia/myopia. Dr. Stark?

DR. STARK: Corneal astigmatism should be considered, otherwise the patients are going to wind up with multiple surgical procedures which may complicate the issue.

DR. WEISS: So, you would like to have astigmatism up to X amount?

DR. STARK: Yes.

DR. WEISS: Up to 7.5?

DR. STARK: I would say probably 1.5 because you will correct 0.75 of a diopter with a corneal incision for the IOL.

DR. WEISS: Okay. Anyone else with? Dr. McMahon?

DR. MCMAHON: Presuming that visual acuity distance and near is going to be part of this. I think there needs to be a minimum level of visual acuity and the standards that are being applied for distance acuity probably are fine. There aren't really good standards for near acuity. We have had one trial that we have seen that I have some questions about that I raised at the last panel meeting in terms of what those standards should be. For example, preop best corrected visual acuity, and for the one trial that I am familiar with there was a certain percentage J3 or better enrolled. Right?

DR. ROSENTHAL: What about distance visual acuity, Dr. McMahon?

DR. MCMAHON: Personally, I would like to see 20/25 or better.

DR. WEISS: Best corrected? So, basically I think you are saying that these people should have excellent best corrected visual acuity and they shouldn't be having other pathology going on, otherwise they should not be included in the study. Does anyone disagree with that?

DR. BRESSLER: Only a comment, going on the same theme of this morning, you know, wanting

to find out how this is going to happen in moderate myopia, minus 8 and minus 10, there are a lot of people out there with 20/32 vision from some slight degenerative changes that may be suffering from their presbyopia and I am not exactly clear why we want this excellent sort of vision.

DR. WEISS: Dr. Mathers?

DR. MATHERS: You might stratify to be slightly more liberal for the high myopes, I would think, say 20/30 or something. If you do 20/80 you are not going to learn as much but you could make it softer for the higher myopes.

DR. BRESSLER: Then I am more comfortable with even 20/40-ish where you can see if there are changes.

DR. WEISS: Dr. McMahon?

DR. MCMAHON: Since the general consensus was that there were active controls, you want to have decent enough vision so that you can tell differences between the groups. If you use either historical controls or preoperative controls, then I think you can have a lot more slip in terms of entrance visual acuity to get to where you want to go.

DR. BRESSLER: My last question is in

terms of diabetic retinopathy, and that is although it is rare, there is documentation of an atypical edema that develops when you have diabetic retinopathy, and it is probably true when you have other vascular abnormalities, like having had a vein occlusion, and should those be included in the mix? Presumably they would be randomly assigned to both sides, but is the risk worthwhile where you have a known event that can affect them and they haven't lost vision from their cataract yet?

DR. WEISS: Dr. Ferris?

DR. FERRIS: I think diabetic retinopathy is actually a point that should be carefully addressed because there is published data showing that this is a group having particular problems with accommodative amplitude, particularly those that have relatively severe diabetic retinopathy. So, it is a group at risk but they also are particularly at risk from a surgery. So, I think some discussion, maybe not here but some careful discussion about whether you are or are not going to include them--and if you are to include them, then I think you need to include enough so that you can actually say something about them.

DR. WEISS: I assume the company in that

case is going to want to exclude those patients because they are not going to improve their data. Dr. Eydelman, did you have any comment on that?

DR. EYDELMAN: Basically the same thing. For device investigation they exclude all ocular pathology.

DR. WEISS: Walter, did you have a comment?

DR. STARK: No, that was the comment I was going to make.

DR. WEISS: Any other comments on this? If the agency is satisfied with the answers to question 2 we will go to question 3. What should be the primary safety endpoint for the study, retinal detachment rates, endothelial cell loss, or any other primary safety endpoint? Dr. Bressler?

DR. BRESSLER: When someone has vision loss so they are having cataract surgery to correct that, all of the litany of side effects that could occur that were given in that FDA grid are at low enough rates that people are willing to undergo that. But I wonder if you have to have some sort of cumulative morbid event as your safety? If you just said retinal detachment then, that alone may not change. But if you said retinal detachment or

cystoid edema or endophthalmitis or features that affect visual acuity, since you are starting presumably with an otherwise normal eye except for the presbyopia, it seems that this is a little different safety question than just safety for cataract surgery when there is vision loss from the cataract.

DR. WEISS: You are saying sort of cumulative--

DR. BRESSLER: Events that affect visual acuity in some way.

DR. WEISS: Dr. Ferris?

DR. FERRIS: Just in general I object to the term primary safety endpoint because if any serious endpoint was reached, I think it would then become a primary one. If there was lots of endothelial cell loss, I don't care whether there was retinal detachment or not, that may be primary. If there is lots of retinal detachment it may not matter how much endothelial cell loss there is. So, I have sort of a general problem with picking one outcome. I know why the agency does that for statistical reasons, but for the harm side I think you are looking at all of them, and maybe the major reason for even doing this study is that you want

to inform patients as to what the risk is so you want to measure all of these risks. Because any risk that you think is clinically important we should be measuring and we should be informing the patients about, and I don't know which one is primary; they are all primary in my view.

DR. WEISS: Would that be satisfactory?

DR. EYDELMAN: No.

DR. WEISS: No?

DR. EYDELMAN: Because--

DR. WEISS: Go ahead.

DR. FERRIS: For LASIK, didn't we have a grid that you had to meet certain criteria for multiple negative outcomes, that you couldn't have worse than this for several different bad outcomes?

DR. EYDELMAN: Yes, you are correct. What we are talking about is different ways of constructing clinical study designs. Primary safety endpoint is the terminology used under ISO for clinical trial design and that is why it appears here. The way it is usually done is you determine the one that, as you mentioned, you base your cohort size and that is why this question is before the sample size and duration determination. So, here we are not asking you which is the only

safety endpoint you will be collecting. We are definitely going to be collecting information on all of them. What we are asking you is which one is important enough to drive the statistics, which one should we base the sample size on, and that is why the answer I got so far doesn't really address that.

DR. WEISS: We have quite a few comments on this. Dr. Maguire, Dr. Mathers, then Dr. Brown, then Dr. Bressler. DR. MAGUIRE: I think one endpoint should be the incidence of secondary intraocular surgical procedures. Is that yes or no? Does that sound like a not good idea to you, Dr. Eydelman?

DR. EYDELMAN: No, I think perhaps panel members are getting confused between question 3 A) and the following question where different adverse event rates for which we should be collecting information are being addressed.

DR. MAGUIRE: Okay.

DR. EYDELMAN: I just wanted to make sure that people are clear on that.

DR. WEISS: You stated it already, but if you could stated it again for the panel, what is meant by the word primary safety endpoint?

DR. BRUCKER: Wouldn't it be the lowest of the incidence rates so that the lower rate would be the retinal detachment which we would expect to be lowest?

MR. CALOGERO: I guess it is using a combination of the lowest rate plus, additionally, your minimal detectable difference--

MS. THORNTON: Don, I am sorry, they are telling me they can't hear you.

MR. CALOGERO: Don Calogero, FDA. We are using this in an attempt to determine the sample size here. So, we have all these adverse events here. Some of them are at very low rates, as you know. But you can't simply pick the one with the lowest rate because that particular event might allow a much larger minimum to detect the difference. So, it really has to be what you want to drive the precision of your study, what endpoint, what is the most important one to drive the sample size. We need that information, that feedback to be able to determine the sample size for the study.

DR. WEISS: So, let me ask you a question. Dr. Bressler was suggesting to, let's say, select a certain number of lines of lost vision from a

variety of causes. Would that be able to drive the study or no? Did I understand you correctly?

DR. BRESSLER: Well, it was a list of events that either affect visual acuity or have the potential to, and those could be defined, but my concern was exactly what you were bringing up in the trial design, that is, if you make it, for example, retinal detachment and you are doing people less than 8 diopters or less than 6 diopters, whatever you choose, I can tell you right now you are not going to be able to detect difference, not that there is one but the event rate is so low you won't be able to detect a safety problem. But if you say to the patient after the fact, well, what is my risk of something going wrong--they are not asking what is my risk of retinal detachment and macular edema and ophthalmitis and needing another intraocular surgery, etc. If those could be defined, I was just expressing a possible opinion of using that as your primary safety endpoint, and then it doesn't have to be that large a study. You are not going into 10,000, you know you are ar 1,000, 400 or whatever.

DR. WEISS: Is that potentially possible

or no?

MR. CALOGERO: It would be an unusual study design. Suppose that results in a sample size of 75. For that particular outcome you can detect a difference between the two groups but it may tell you absolutely nothing about much more specific ones, say the retinal detachment rate when it is small. Even if you use the historical control, essentially close to 0.1 percent, 0.3 percent, your minimal detectable difference with that sample size may turn out to be 5. So, for that adverse event you can only say with any confidence that it is somewhere below 5 percent if you don't see it in the study. If it is above 5, then it is different than that.

Later on in this presentation we look at actually slides that go into what you can detect, the sample sizes, so even for the low adverse event rates for retinal detachment if your minimal difference is large enough--it reaches a point, of course, where the study size does become reasonable. So there are two things you have to weigh there. It is unfortunate this whole discussion is sort of like a circle; you have to look at all these factors simultaneously.

DR. BRESSLER: I do understand that is why I am concerned because I think, if I were testing this, I too would probably design a trial where I am only going to include people where the event rate of that retinal detachment is down to 0.1 percent, or something, by saying no one over minus 6 diopters or something. As a patient, we want to know what is our risk of these other events.

DR. BRUCKER: And the other--

DR. WEISS: Dr. Brucker, we are going to go with Dr. Mathers, Dr. Brown and then we will be coming back to you. Was there anything else you wanted to say on that point? No? Dr. Mathers?

DR. MATHERS: I think there are really only two options, either it is the retinal detachment rate or it is the endothelial cell count. The endothelial cell count is going to be a much softer endpoint that occurs way late in the game. It is not going to be useful to do that if you are talking about a study that is only three years long, or whatever, and retinal detachment is a reasonable thing to look at. From the examples that you gave us here, you can design a study that has a reasonable power for a fair sized population and I think that is what you should do.

DR. WEISS: Dr. Brown?

DR. BROWN: I basically concur with that. In terms of what we are trying to do as a primary safety endpoint, and as everyone has said there will be secondary endpoints that will also be looked at, but in terms of the primary safety endpoint, the numbers that you presented in your grid don't seem extreme and I think that that should be in part because of the implication of it and in terms of later loss of function and because of the lack of data that we don't have in some these areas of refractive error, I think that that should be the primary safety endpoint.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: What was the safety endpoint used for the original approval of the IOL?

DR. EYDELMAN: Endophthalmitis, rate of endophthalmitis for the monofocal IOL.

DR. BRUCKER: So, the rate of endophthalmitis in this study would probably be higher than the projected rate of retinal detachment in this study. So, would it be reasonable to then look at endophthalmitis as a primary safety endpoint?

DR. EYDELMAN: Probably not because--

DR. BRUCKER: Could you put that up again? Or, it is not worth it I guess.

DR. EYDELMAN: I just want to make one point, what I stated before, most likely we would entertain clear lens IOLs for clear lens extraction after the establishment of the safety and efficacy in the cataractous population. So, what we are trying to say is that if a sponsor established that their MIOL is safe after cataract extraction, then it is hard to say that when you take the same exact material and the same exact MIOL and the only difference for the population is that the rate of endophthalmitis is going to be different. So, we want to try to avoid the situation where a sponsor comes in and claims there are no additional safety endpoints to establish.

DR. WEISS: From what I hear from the panel in terms of what primary safety endpoints you can actually use, it seems like retinal detachment is the one that was most frequently mentioned by the members of the panel. If that is sufficient for you--

DR. BRESSLER: Can I make one other comment?

DR. WEISS: Yes, Dr. Bressler?

DR. BRESSLER: I just want to point out that we have on the grid this 0.5 percent of retinal detachment but it has been pointed out by Dr. Lane, and it is true I think if you look in the literature, that if we exclude a certain degree of myopia it could be as low as 0.1 percent. So, you have to take a 0.1 percent level and put that into the mix as well.

DR. WEISS: Okay, I see agreement by the agency. We will go on to part B)--Malvina?

DR. EYDELMAN: I am sorry, since you agreed on minimal endothelial cell density as preop criteria, perhaps you could look at the table on your left to give us some guidance as to what cell density at age 75 you recommend and then we can calculate back as to the inclusion criteria.

DR. WEISS: This is sort of an additional thing while we are on this topic. Any comments from the panel as far as whether you want 1,000, 1,200, 1,400 or 1,500 cells left at age 75?

DR. EYDELMAN: Thank you.

DR. WEISS: Walter?

DR. STARK: I am going to pass.

DR. WEISS: Pass? Bill?

DR. MATHERS: I think 75 shouldn't be

considered the end of life for these people. They probably have 20 more years to go. We should go to the higher count, 1,500.

DR. WEISS: So, 1,500. Dr. Grimmett?

DR. GRIMMETT: I concur with 1,500.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: What was used in the prior studies of the anterior chamber IOLs?

DR. EYDELMAN: We weren't that advanced then.

DR. BRUCKER: So, we have no information from prior studies.

DR. WEISS: Seeing no other comments, the only two comments voiced have been for the higher levels of 1,500. Now we will go on to part B) of question 3. What should be the acceptable adverse event rate associated with the safety endpoint, which I think we have defined here as being retinal detachment rate? Dr. Bressler has mentioned that it would be more towards the 0.1 because certain degrees of myopia might be excluded. Dr. Ho?

DR. HO: I agree in general with Neil's comments but we have to be a little bit careful because those comments are based on cataract surgery in older patients and age is a relevant

risk factor here. Let's say the average age for a cataract patient might have been 65 years, we are talking now about somewhere between 50 and 55 years or 40 and 50 years, and you could be surprised with a little bit of a difference there.

DR. WEISS: Dr. Bressler?

DR. BRESSLER: The younger ones though may have had the higher rate if you controlled again for their refractive error. So, we do see younger people who are higher myopes come in with their posterior capsular opacity, etc. I think that was again referring to Dr. Lane's presentation, saying that if we exclude some of these we are really going to have a lower event rate.

DR. WEISS: Dr. Ferris?

DR. FERRIS: So, the corollary to that is that if you are going to set a retinal detachment rate you may want to set a different rate for non-myopes and myopes because the underlying rate is going to be different.

DR. WEISS: So, it sounds like we have to set it for the high myopes, lower myopes and hyperopes, or low myopes and hyperopes versus higher myopes?

DR. FERRIS: Yes, just the two.

DR. WEISS: And do you want to suggest what rates you would want for those, what numbers? Dr. Brown?

DR. BROWN: I have spent some time thinking about that beforehand and the 0.3 percent per year, from reviewing the data, seemed to be reasonable for the myopic population. We wouldn't want to go beyond that. But the other thing that this does imply if we separate, which I think we should do, is that we are going to have to make sure that the sponsor stratifies the population. We need strict requirements, we need this many patients within this refractive range and this many patients within this refractive range for it all to play out.

DR. WEISS: I think that is a good suggestion so you won't be in a situation where you have minus 15's and we don't have enough data. Is that sufficient information for the agency? Well, since they are discussing it, it sounds like not. So, anyone else have any comments on this particular issue? Dr. Brucker, do you have any comments on the retinal detachment rate?

DR. BRUCKER: Dr. Ferris just said that we had said that a couple of hours ago. I think that

is the proper way to stratify it. I think that is correct.

DR. EYDELMAN: Perhaps as we go to 4 A) that will be clarified a little.

DR. WEISS: So, what is missing for you, Malvina? What haven't you gotten from the answer from the panel on this one?

DR. EYDELMAN: The number.

DR. WEISS: So basically, bottom line, you want a number from us as far as what we are looking for the high myope rate versus the rest of the population.

DR. EYDELMAN: What would be acceptable. I think perhaps looking at the table on the left in conjunction with question 4 A)--again we are in this circular logic but I think what we are looking at is the maximal allowable retinal detachment rate that you would find acceptable. That drives the sample sizes so if you now start breaking it out into different subgroups, then we would have to have that number of subjects for each indication.

DR. WEISS: Basically, if the panel is willing to agree to a higher percentage, then the study enrollment goes down.

DR. EYDELMAN: Yes. Again, you can do it

by sub-indications or as a group.

DR. WEISS: Dr. Ferris?

DR. FERRIS: Did I miss in a previous slide that for that endothelial cell count that we were already over 1,000?

DR. WEISS: Well, I think these are two separate pieces of data.

DR. FERRIS: Well, no, they are not. If you have a 1,000 then you have enough to look at retinal detachment.

DR. EYDELMAN: No.

DR. FERRIS: What do you mean, no?

DR. EYDELMAN: No, because you have determined that you want the retinal detachment rate to be the primary endpoint and the endothelial cell was as an inclusion criteria. In other words, all we said was we are going to calculate back and figure out what minimal endothelial cell loss the subject would need in order to end up with that.

DR. WEISS: We are not determining enrollment based on that graph even though they had information on enrollment based on that graph. Is that correct?

DR. BRUCKER: The graph says 113 patients and 1,500 cells. It doesn't as go as high. If we

used 0.3 here we would need 321 patients. I think that is the question he was asking. It is not over 1,000.

MR. CALOGERO: It depends on the duration of the study. For the one-year study it is over 1,000.

DR. FERRIS: Then I agree with what you said. That is why I said I wasn't sure what whizzed by--

DR. EYDELMAN: We are going to see it again in a minute.

DR. WEISS: So, Dr. Ferris, you are okay and, Dr. Brucker, you are okay?

DR. FERRIS: I am okay, except I am totally lost. We haven't come up anywhere near--and the reason we haven't is that it is a complex issue and we don't have all the numbers in front of us. I am glad you have these numbers because that is what we need to drive this because we say they are all important and we want to make sure that we pick one of the important ones, sort of the least common denominator here. So, you have to look at them all in combination and that is why we are struggle. That is why I struggle because I thought what whizzed by was 1,500. Well, if it

1,500 we are done. But if it is 100 we are nowhere near done.

DR. WEISS: Unfortunately, you are not done yet.

DR. FERRIS: Right. My view is that if retinal detachment is the driving one, then we need to look at two groups. We need to look at the high myopes and in each of those groups you have to have adequate samples.

DR. WEISS: Yes, basically I think I just hear consensus on that. I think what Malvina wanted is, okay, we agree that there have to be two different groups but it would be helpful to her if we gave some number for these two different groups. Dr. Mathers had a comment. Was it addressing that, Bill?

DR. MATHERS: Yes. Are we assuming that for the non-high myopes the normal retinal detachment rate is about 0.01?

DR. EYDELMAN: Yes.

DR. MATHERS: So, 0.1 would be ten times higher?

DR. EYDELMAN: Yes.

DR. MATHERS: And 0.1 would be a pretty high number and it is already ten times higher.

So, 0.3, 30 times higher than the normal rate is too high, right?

DR. BRUCKER: But that is exactly the reason--

DR. WEISS: Dr. Brucker, could you hold it? Have you finished?

DR. MATHERS: So, I would go down on the left side of the chart.

DR. WEISS: So, you want to go to what number?

DR. MATHERS: 321, three years and the lowest number there, the lowest allowable detachment rate.

DR. WEISS: That is not the lowest allowable detachment rate. Malvina?

DR. EYDELMAN: That would allow you to detect maximum of 0.3 percent annual loss in a three-year study.

DR. FERRIS: So, that is one retinal detachment.

DR. HILMANTEL: Can I say something here?

DR. WEISS: Yes.

DR. HILMANTEL: These numbers are calculated--I am sorry, I am Gene Hilmantel--these numbers are calculated to try to get the minimum

size that let's you detect that rate, but there is a caveat here. For most of these, especially with the lower rates, the study would only pass the endpoint if you got zero retinal detachments. So, if you want to have a study that would permit one or more retinal detachments and still pass the criterion, you have to have a larger sample size than in the chart here.

DR. WEISS: Basically practically, the smallest percentage we could define in this, let's say for the non-high myopes would be 0.3 percent?

DR. HILMANTEL: That is correct.

DR. WEISS: So, the 0.1 percent which was brought out by more than one person is not something you would be considering. The least rate that we could consider as the panel is 0.3 percent. So, let's just address that.

DR. HILMANTEL: I mean, you can consider whatever you want to--

DR. WEISS: But it wouldn't be practical.

DR. HILMANTEL: --but the smaller it is, the larger is the sample size.

DR. WEISS: Okay, so if it is not practical, we can deal with that.

DR. ROSENTHAL: It is not that it is not

practical, if you feel that a retinal detachment rate of one percent is acceptable, then it is acceptable. If you feel that it is not acceptable and 0.3 is acceptable, that is what is acceptable. So, we need to know what you feel is an acceptable retinal detachment rate.

DR. WEISS: Well, what was brought out previously was 0.1 percent.

DR. ROSENTHAL: That makes the study enormous.

DR. BRESSLER: And that is why I wasn't voting for retinal detachment being a primary safety endpoint because it is going to be impossible to do.

DR. WEISS: Dr. Ferris had a comment and then Dr. Brucker. Dr. Eydelman?

DR. EYDELMAN: I just wanted to point out that our cumulative RD rate from the FDA grid is 0.3 percent so the chances are you are not going to be way--

DR. WEISS: Way far off from that. We are going to have Dr. Ferris, Dr. Brucker and then Dr. Ho. Dr. Ferris?

DR. FERRIS: I guess I am a little confused now with the maximum allowable retinal

detachment rate. If your expected number is one detachment and you get one detachment, you have no idea what the rate is. If these 321 people bought lottery tickets and somebody one, the rate of lottery ticket winning would not be 0.3 percent. We need at least a couple of events to be able to say anything about retinal detachment. I also agree with what Neil was saying, that is, it may be unreasonable to power a study to get an accurate assessment of retinal detachment rate. So, somehow there has to be a balance between reason and what you would like.

DR. WEISS: Dr. Brucker?

DR. HILMANTEL: Can I say something?

DR. WEISS: Yes.

DR. HILMANTEL: Gene Hilmantel again. In this type of pre-approval study, you are absolutely correct, the only thing you can demonstrate really with any confidence is that the rate is less than a certain maximum allowable rate that we would select. To really get a handle on the rate you need many more patient years and that can probably only be addressed in a post-approval type of study.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: Yes, I think that the

problem is that when you talk about the rates and you have 0.3 most people might say that is fine for the entire cohort. But now you are talking about splitting them up, and if you start to split them up and you only have one rate we are not saying that you are going to look at them all with the same end rate. So, if you wanted to go down to 0.1 you would be at 1,000 patients or whatever it is, it is too many. So, you are going to have to go back and recalculate. You are asking us for a number and that is not what we are offering you. We are telling you as doctors and surgeons that that rate is going to be extremely, extremely low and we don't expect that. This is an acceptable rate if you take a look at the whole cohort. One percent is unacceptable. If now your rate, as Rick was saying, is zero in the series of patients that are done that are medium myope and emmetrope you will have no retinal detachments, in other words, and you got one or two in the other group, the high myopes, that is going to be all right but you are going to be analyzing them separately. So, you can't keep asking us what is the number; what is the number if you are going to analyze two groups separately. Do you understand what I am saying?

DR. WEISS: But can't you just give two numbers?

DR. HILMANTEL: You can give us guidance if you want.

DR. BRUCKER: The point is that the 0.1 for the emmetropic patient would give you 1,000 patients which is unacceptable. If you go up to one percent in the high myope, that also is too high. So, you are going to have to look at the aggregate number; 0.1 percent is too high and 0.1 gives you 1,000 patients. We can't design a study based upon that. Now, if you wanted to ask everybody in this room whether they think it has to be less than one percent retinal detachment rate regardless of the group of patients being looked at. Does that make sense?

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: It makes sense but I am just trying to get further guidance. I mean, what we are saying is that you have a different maximum allowable rate depending on the population.

DR. BRUCKER: Right.

DR. EYDELMAN: That is fine. What we are asking you is tell us, please, what the two populations are and what would be the maximum

allowable rate for each of the populations. Then we can go ahead and design a study around it.

DR. BRUCKER: So, Neil and myself would respond to you by saying that had you made a table--and these tables are wonderful; I congratulate both of you for doing this--had you made a table, one of them being from emmetropia to, let's say, minus 6 and the second table from minus 6 to minus 16 you probably would have had two numbers because the literature that you have described gives you different retinal detachment rates. But you didn't give us that; you are only giving us one aggregate and we can't give you an answer because we don't know the number.

DR. WEISS: Dr. Ho?

DR. HO: I was going to echo Sandy's comments precisely. I think that if you look at the literature you presented, there is one study of 52 myopes where the retinal detachment rate was an astounding 2 percent at 4 years and then up to 8 percent at 7 years. This conversation is beyond my comfort level to start with for clear lens extraction for presbyopia. I am way on the left over here and way down in numbers of years. I understand the limitations. I think this is a very

significant public health issue. I think there could be many thousands, millions of patients that could be--seduced is maybe not the right word but that would be enticed by advertisements of throwing your glasses away. I think we need to be more careful here. If you ask me for numbers I would say for the general group 0.3 is probably okay; for the myopes, you know, something a little bit higher but not too much higher.

DR. WEISS: I understand what Dr. Eydelman is asking us for and I understand the sentiments on the panel but I still think we can get more in the direction of what you are saying, not an exact number but I would assume that everyone here would agree that you wouldn't want to be higher than one percent for the high myopes. Would anyone disagree with that? Would anyone want to have a higher percent than one percent RD rate for the higher myopes? So, one percent would be the maximum for the high myopes.

DR. HILMANTEL: Can I just clarify?

DR. WEISS: Yes.

DR. HILMANTEL: That wasn't the rate per year. So, if it is one percent per year over ten years it would be ten percent.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: I think starting with Dr. Lane's presentation this morning and everything I have heard from our esteemed surgeons here, the impression I get is that the lens extraction procedure is now so safe that with reasonable numbers you are not going to be able to evaluate whether a particular clear lens extraction product or lens that is going to be put in is going to elevate the hazard by any reasonable amount. You are simply not going to be able to evaluate that because the procedure itself is so safe. All you can do with these numbers is essentially screen for a disaster; you cannot evaluate whether there is a reasonable increase in hazard because the procedure itself is so safe. It can only be done post-market with large sample sizes. But I believe these numbers seem reasonable as a screen for a disaster basically and I think what the people around the table are saying is that the number of 0.3 percent sounds about reasonable.

DR. WEISS: The agency will speak, obviously, but I am going to think that Dr. Bradley's comments should probably be the bottom line here, that most people have voiced 0.3 percent

so why don't we leave it at 0.3 percent and you can see that there is a lot of discussion and discomfort on this issue? Do you have any comments on this?

DR. HILMANTEL: Yes, my only comment that one of the questions we are asking you in essence is, is this something that we should look at in a pre-approval study, given that all we can do is establish that the rate is less than a certain amount?

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I am going to look at it from a patient standpoint. You can look at it two ways, you can say a low incidence of retinal detachment or you can say my risk of retinal detachment is five or ten times higher over X period of time if I have this done than if I don't have this done. That is how patients think about it. Okay? And, we are talking about incidences 10 or 30 times higher and barely being able to detect it. I also understand that if we did a study to be able to detect something 3 or 5 or 10 times higher than expected, it would be too many patients.

So, what that tells me is that the public health effects of clear lens extraction and retinal

detachment are not going to be elucidated by any pre-approval study by the FDA. It is not going to happen. So, there is a potentially serious public health effect if clear lens extraction in pseudophakic IOLs that will remain after this study goes. It will have to be addressed elsewhere.

We had absolutely no analysis from Dr. Lane on how he came to the conclusion of retinal detachment when the confounding factors were removed. I am not at all sure if he included YAG laser capsulotomy in that or not. If that was an issue, obviously that can be up in the 30 and 50 percent.

DR. WEISS: Because of interest in time and we have five more questions to get through and less than an hour to do it in--I still hear the sentiment from the panel that that should be included. The number is controversial but 0.3 percent has been mentioned more than once. If that is satisfactory for you we will go on to question 4.

DR. EYDELMAN: And I understood 3 is pre-PMA because the question was twofold, percentage and the number of years before the PMA. I saw a couple of people pointing to number 321

which implies 3 years.

DR. WEISS: In 4 (A, are we not going to get to the duration of the study?

DR. EYDELMAN: No.

DR. WEISS: Because in 3 I didn't think the amount of time for the study was being addressed, unless you want us to address it now. It just said adverse event rate.

DR. EYDELMAN: No, we were discussing 4 (A.

DR. WEISS: No, we haven't gone to 4 (A yet or, if we did, I didn't know it. Maybe I missed it. So, you want us to get involved in the duration of the study.

DR. EYDELMAN: It was a conjoined effort.

DR. WEISS: Is there consensus that it should be three years? Dr. Ferris?

DR. FERRIS: I would say three years is a good minimum length for the study, and I was going to make a suggestion with regard to a slightly different approach to sample size, and that is that I think people would like to know if there is a one percent risk, and I think you could power the studies so that you would have enough power to give a reasonable estimate of the absolute risk.

There are two issues here. One is the relative risk and one is the absolute risk. The absolute risk is almost uninterpretable by patients because one percent, a tenth of a percent or a millionth of a percent--they think it is very low. So, it seems like you need some sort of confidence as to what the actual rate is so you can say it is one percent but that is ten times higher than what you would have if you don't have this procedure. I think you need both numbers, and you need enough cases to have some confidence about what that number is. The 321--I am glad someone else pointed out that I don't read the graphs very carefully because it is per year so that is actually three cases. I think you can do the math; the agency can do the math to get some sort of reasonable confidence because I think the most important thing we are going to do is to be able to tell these patients what their risk is and you need enough patients to be able to tell them what the risk is, and then the Admiral Farraguts can go ahead and the Hamlets can think about that and not do it, but at least they would have something to base their determination on.

DR. WEISS: Dr. Stark?

DR. STARK: But if we are going to have two groups, the mid-myopes and the high myopes, then we are talking about twice that number. Could we compromise and say 0.3 for the lower myopes and hyperopes and 0.5 for the others? That would give a total of a little over 500 patients, which is what the cohorts have been in the past.

DR. WEISS: Dr. Ferris?

DR. FERRIS: I am sorry, I did the math for the non-myopes. The math for the myopes is going to be a smaller number because you are going to have more events. So, you would need maybe a third of the number or less because their rate is something like one percent per year so you are going to need a much smaller number.

DR. WEISS: That is a good point, Walter. Three years is what we are talking about, it seems. Dr. Bressler?

DR. BRESSLER: I just want to make a discussion point about potentially considering two years. Most of the literature, to my knowledge, suggests that complications that happen after cataract surgery happen within a year's time. So, by going to two years we will catch them, if there were some additional problems going on. But it

gets more and more expensive and less likely to get follow-up as you try and get these people out to three years. So, I am not sure we need that third year.

I will point out that in the clear lens extraction minimum data that FDA presented this morning, which was very helpful, that 8 percent rate was because there were some detachments happening at three, four and five years after the cataract surgery and these were high myopes. So, it is not clear in my mind if that is just detachments that were going to occur due to the pathologic myopia anyway. We just don't have any strong data to suggest that there is an increased retinal detachment rate beyond the one to two years. So, I am just suggesting that you could consider two years.

DR. WEISS: Just for members of the panel, for those who were at the last two meetings, we always get involved in these difficulties with endothelial cell loss. That probably won't be an issue here because it is a standard operation, but the less number of years of data you have, the more difficult it is to try to figure out what is going on.

DR. BRESSLER: I was only talking about retinal detachment.

DR. WEISS: You know, that is something the panel can discuss.

DR. BLUSTEIN: Could I say something?

DR. WEISS: Yes.

DR. BLUSTEIN: This is Joe Blustein from the FDA. The relative risk for retinal detachment is greatest within the first year. It is about 10-20 times greater having cataract surgery than not, but it still continues out and after 4 years it is still 6 to 7 to 10 times greater than not having surgery. So, the risk of retinal detachment persists even beyond that first, second and third year.

DR. WEISS: Dr. Ho?

DR. HO: I would echo those comments that were just made. I think I would be comfortable with a shorter follow-up for those patients that are less at risk, that is, those that are low myopes, emmetropes or hyperopes that we have included. But I would like to see longer studies, particularly considering some of the literature that is out there for the higher myopes.

The other issue is that the cataract

surgery results are for a group of patients that are older. This is clearly a different set of patients and if you are younger and you are more myopic I am not as comfortable with two years. I think I would be reasonably comfortable with two years for the non-highly myopic group.

DR. WEISS: Dr. McMahon?

DR. MCMAHON: I would like to support Dr. Bressler's view. At several of these types of meetings where we have tried to look at these shallow slope differences, we are always left with a quandary and I think we have an opportunity here, since the majority of the retinal detachment risk associated with the surgery is in the first year or so, of shortening the Phase III trial. But then I would like to argue for a detailed post-market study for a much longer period of time to pick up those sorts of things. That is exactly where that prospective case control kind of thing can come into play that I mentioned earlier.

DR. BLUSTEIN: In the large cohort studies about 40 percent of the retinal detachments occurred within the first year, and then 60 percent occurred within years two to three or four and that was the length of those cohort studies. That is

just information.

DR. WEISS: What I am beginning to hear is sort of a trend, especially in view of the primary safety endpoint of retinal detachment, that a two-year study with post-market follow-up would be sufficient. Does anyone have any disagreement with that? Dr. Mathers?

DR. MATHERS: There would be an advantage in endothelial cell count to look at a three-year point, and I am going to predict that 40 years after the operation the endothelial cell count is going to be the more important number than the retinal detachment rate. So, I would argue for three.

DR. WEISS: But would you be averse to having that post-market?

DR. MATHERS: That is fine.

DR. WEISS: Because we could still include that in post-market. Dr. Ferris?

DR. FERRIS: Just one last comment, although I agree with you that the endothelial cell count is going to be important, remember that the retinal detachment rate, as was pointed out, doesn't stop. So, when you multiply 25 years, 30 or 40 years times that, that is going to be a

pretty ugly number too.

DR. WEISS: Dr. Stark?

DR. STARK: I think in the original study, the standard study, I would like to see a little longer than three years to ensure that we are not opening Pandora's Box here. There has not been a lot of clear lens extraction in 40 year-old normal people. But with the tight vitreum- retinal adhesion in those patients the fact that we are going to be jarring that, maybe separating it and causing some retinal detachments we may see an unusually high number of retinal detachments in these people and thinking, well, no, they were just supposed to be the myopes that got the retinal detachments.

So, I am a little concerned about it. You know, when you see the cataract patients you look at them and, as a clinician, most of the myopes and the young cataracts will have vitreous detachment already and that may be contributory to the cause of the cataract. There may be an association. So, this may be an entirely different group of people that have a very tight vitreum-retinal adhesion. So, I would rather see the three years. What I would to ensure though is that we get that

post-approval follow-up on those patients in high numbers because I think if something still can be done, or at least the public education, if four and five years out--Joseph Colin criticized the Italian group for saying that there was a high rate of retinal detachments in these patients at four years because he only had two percent, but then it went to eight percent at eight years. So, I think we just want to make sure we are not missing a big problem.

DR. WEISS: So, agency, I think you can hear the mixture of opinions, somewhere between two and three years and I think the points you raised here are important ones about the vitreous and younger patients.

We are going to go on to B), do you believe a post-market study is indicated? I am going to answer that. The impression I get from the panel is that most people are talking about a post-market study. If so, what is an appropriate type of study, sample size and length of follow-up for such a study? That is all going to get answered in about the next four minutes. Anyone have a quick answer for that one? Walter?

DR. STARK: If you are just looking at

retinal detachment events you should be able to pick that up and visual acuity and YAG laser capsulotomy probably. So, I would say five years.

DR. BRESSLER: I would echo that--

DR. WEISS: Dr. Bressler?

DR. BRESSLER: I am sorry, yes, as you go beyond five years in this age group, they start moving around and you can't even follow them and I don't think you will have data to interpret as well, so to be reasonable with what is expected and what we are looking for, I think five years is a good number.

DR. WEISS: Dr. Blustein?

DR. BLUSTEIN: I think you need to be aware that a post-market study doesn't necessarily mean following the same cohort that was in the PMA. It can be following a new cohort once this lens is out in the market or a sample of that cohort and it can be followed for five years or longer to see what complication rates are.

DR. WEISS: So, Dr. Start and Dr. Bressler, when you were speaking about five years did you mean the same cohort?

DR. BRESSLER: Not necessarily.

DR. WEISS: Not necessarily? And would

you want a new cohort followed for a five-year period of time or would you like to follow the same cohort?

DR. EYDELMAN: Well, it depends on the N.

DR. BRESSLER: Right. You would probably have to add to that cohort because, right, you wouldn't have enough.

DR. WEISS: Dr. Blustein?

DR. BLUSTEIN: Comments that have kind of come to the panel in the past about this is in the hands of the best surgery on a group, and it is a whole different issue once it gets out there into the market. I think that you have to take that into account too, that retinal detachment rates, complication rates may be very low in this cohort but once it is out in the market it might be a different issue.

DR. WEISS: So, you are bringing up the point that it might be beneficial to have a new cohort and you would want to know from us how many years and what is the sample size. Is that correct?

DR. BLUSTEIN: Correct.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: I just wanted to comment

that it is fairly obvious that there are two approaches you can take, both of which you have mentioned. You either follow the existing cohort out to whatever time you feel appropriate or you set up another type of study. Now, the other study can't be as intense as the existing study. I think this panel has been told several times that there are other ways of doing post-market studies. For example, with the 30-day contact lens there was a very large number of patients being enrolled for a reasonable--I forget what the time frame is, in which only major events are being reported. It seems to me a similar type of post-market study could be arranged here where you enroll so many patients and you look for major events. We are not interested in visual acuity; we are interested in whether or not they have had a retinal detachment or whatever else you are interested in.

So, you can approach it either way and we need the panel's input on which way do they think is the best way to approach it.

DR. WEISS: Dr. Blustein, Dr. Mathers, then Dr. Stark and Dr. Ho.

DR. BLUSTEIN: You don't have to be specific about length of time to follow and sample

size. That can all be handled through the agency. We just need to know the events of concern that the panel wants to address.

DR. WEISS: I think the one event of concern that everyone is bringing up is retinal detachment. Dr. Maguire?

DR. MAGUIRE: The one event that definitely would need a separate population is removal of the lens or other secondary intraocular procedures down the line. I think it is very wise to look at what we have learned from cataract extraction with presbyopic correcting lenses in cataractous patients. One thing we found with the Array lens is that even though in the initial cohort there was a sizeable class that were unhappy with their procedure. They didn't elect to have them removed when it went into general circulation. About that same percentage that were unhappy now decided to have their lens implant removed, five or seven percent. So, I think absolutely we need that.

The other thing is that we need to have a fairly long period of follow-up because we don't know if the accommodative efficacy will remain stable and if the degree of optical degradation in

some of these lenses will remain tolerable after the initial period of euphoria.

DR. WEISS: Dr. Mathers

DR. MATHERS: I agree with those comments and also you are going to need to measure endothelial cell count and the longer duration you have the better because you are trying to draw an extrapolation over 40 years, and you simply can't do that on a three-year time point. I think that is going to be important.

DR. WEISS: The other thing that I would mention, which was mentioned by a panel member before, is YAG capsulotomy. I think you mentioned that, Leo. Dr. Ho?

DR. HO: They covered it.

DR. WEISS: Dr. Stark?

DR. STARK: I was just going to say that YAG laser capsulotomy increases the risk of retinal detachment by about three times. So, we have to know that number and it might be nice to know that number out to five years so I would think that if you could follow a subset of the original cohort.

Also, the other thing that would be nice to know, and maybe by ultrasound to obtain it, is what is the status of the vitreum before these

surgical procedures and what happens afterwards.

DR. WEISS: I think the endpoints we are talking about are retinal detachment, secondary intraocular lens procedures, YAG capsulotomy. Anything else you need to know from us on this question? Dr. Brucker?

DR. BRUCKER: I guess once it goes out into the public for a new cohort, you may look at retinal detachments but you may have a lot of broken capsules by other surgeons. So, it might e worthwhile to make sure that you have intraoperative complications so that you know how to interpret the retinal detachments.

DR. WEISS: Yes, I think that is an excellent point because your rate of RD goes up by five percent or something. Are you okay, agency, on question number 4? If so, we will move to question number 5.

DR. EYDELMAN: So, there was basically no consensus on the sample size or follow-up? Correct?

DR. WEISS: What I understood the last comment to be is you didn't need the sample size from us but the follow-up, from what I was hearing here, was about five years.

DR. EYDELMAN: We don't need the sample size if we have a rate.

DR. WEISS: A rate of what? Retinal detachments?

DR. EYDELMAN: That we are trying to detect. It is one or the other.

DR. WEISS: Would anyone be averse to suggesting the same rate that we had for the study? Would there be any objection to that?

DR. MAGUIRE: I think it should be lower. I think we should think in terms of relative risk of retinal detachment and other things happening compared to baseline.

DR. WEISS: The problem that Dr. Brucker introduced is that the level of surgery may go down so to expect the complication rate to go down might not be practical. Dr. Bressler?

DR. BRESSLER: But I think we want to inform the public what is their minimal risk that we are reasonably sure that they are taking on from this post-marketing survey. Because we can't do that from the original trial that is planned. From the original trial we can say, let's say for the non-high myope, okay, your risk is no greater than 30 times, you know, retinal detachment. To me,

that is all that we can get out of that original trial but that is not acceptable for the safety of the tens of millions that this could apply to.

DR. WEISS: So, do you have a percentage? Would you want to go back to the 0.1 percent?

DR. BRESSLER: I would actually go even lower, 0.05 and say, well, your risk is not greater than times what your retinal detachment rate is.

DR. WEISS: Dr. Maguire was agreeing on that. Is that acceptable to the agency, just to say 0.05 percent retinal detachment rate with five-year follow-up? Dr. Stark?

DR. STARK: How many patients would you need?

DR. WEISS: Well, I think what they were saying is that the amount of patients would be driven by the percentage of the primary safety endpoint. Is that correct?

DR. EYDELMAN: Right. What we are saying is there are two ways you can do it. You can either tell us the sample size, we think if 2,000 eyes are followed for 5 years it will give us enough information. Or, you can tell us the rate that you want us to figure out--

DR. WEISS: So, Dr. Bressler and Dr.

Maguire who were agreeing, would you prefer to go with a percentage or would you prefer to define a sample size?

DR. BRESSLER: I like 0.05 and following out to five years. My guess is that it will end up being about 2,000 people followed in this post-marketing survey.

DR. WEISS: Dr. Stark, were you in agreement with that way of going about it?

DR. STARK: Yes.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: Just to clarify, are you saying that you think that it is worthwhile in a post-marketing surveillance to follow these patients at a more stringent level? You are saying 0.5?

DR. BRESSLER: No, 0.05. I am just looking for retinal detachment, and 0.05 is five times what their expected retinal detachment rate is if they had not had the surgery. So, we can tell them you are not taking a risk any greater than five times the risk. Is that what a reasonable person might want to know in doing this?

DR. WEISS: Dr. Ho, yours will be the last comment on this particular thing because we are

running late.

DR. HO: I think the public needs to know. I think we will have incomplete information on informed consent which, in my opinion, is really why we are here and it is still a "buyer be aware" situation. But I think the public looks at the absolute rates more than they do the relative rates. Is my chance of infection 1/100? Okay, I will make my judgment. Five times 1/10,000 is less meaningful obviously. So, I would be comfortable for a large number of patients over five years and I would be comfortable with, let's say, 2,000 patients over five years.

DR. WEISS: I think we are all saying the same thing so we can move on. We are talking about 0.05 percent or the rate or approximately 2,000 patients and they may be coinciding. You are not fine with that?

DR. EYDELMAN: No, I am fine with that. I have just been told that 2,000 will not do it.

DR. WEISS: How many will do it?

DR. EYDELMAN: We don't have the numbers but from what I hear they will be much higher.

DR. WEISS: Dr. Stark?

DR. STARK: I was just going to ask is

that too onerous for the companies? They will say, well, fine, we will just to continue to use it off-label. You need to get a little input from the companies about what they would think they could possibly do; 2,000 people followed for five years is a lot of patients.

MR. MCCARLEY: And it is times two because you divided that into two groups.

DR. WEISS: So, we would have to have 4,000 patients--

MR. MCCARLEY: More than 4,000.

DR. WEISS: Basically, by creating a 0.05 percent that is still too onerous. That is what you are saying.

DR. EYDELMAN: Well, it is definitely your recommendation whether it is too onerous or not. But we are saying it is going to be a very large sample size.

DR. BRESSLER: Although the market may be tens of millions of people.

DR. WEISS: Dr. Ho, and this will be the second last comment for Dr. Ho.

DR. HO: I would strongly echo Neil's sentiments there, the market could be much more significant and we need to do that. I will give

you an example, we had a new treatment for patients with macular degeneration. We followed over 4,000 patients for a shorter time period but, again, you need that N to get the numbers.

DR. WEISS: So, there is consensus. I will leave it at that. Question 5, acceptable adverse event rates for posterior chamber IOLs at one year following cataract extraction are listed in the FDA grid. A), are these rates applicable for correction of presbyopia in non-cataractous eyes via clear lens extraction at one year postop? So, do you want to use the same rates in clear lens extraction as are listed on the FDA grid? Dr. Stark is nodding yes. Dr. Maguire is nodding no.

DR. STARK: I wasn't nodding.

DR. WEISS: You weren't nodding?

DR. STARK: You were trying to speed this along!

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I am not saying what number it should be but if you are looking in terms of public health effects, people that have serious persistent problems starting at a younger age has a much bigger impact, especially in a working population. So, I think we should be more

stringent.

DR. STARK: I agree, and the cumulative--cumulative, not transient--cumulative macular edema of three percent is too high to be acceptable for clear lens extraction.

DR. WEISS: I would also agree. You always have to weigh risk/benefit and even though people find such difficulties with presbyopia, I still think the benefit is less than if you had a visually significant cataract so we have to look at the risk a little differently. Is there a consensus that the grid should not be the same as what is applicable for cataractous eyes? If there is consensus, do you need anything else from us on A)? Please don't tell us you need percentages in each category. He who hesitates is lost, Malvina, so we can move on to number B).

DR. EYDELMAN: Well, number B) asks for percentages.

DR. WEISS: Oh, I see. Should acceptable adverse event rates be adjusted for study duration? If yes, how? These were for one year, correct?

DR. EYDELMAN: Correct.

DR. WEISS: Now we have three years in non-cataractous eyes. Does anyone think the

study--well, obviously we all do. So, now you need to tell us numbers?

DR. EYDELMAN: Hopefully. I mean, you can pick one or two categories.

DR. WEISS: Dr. Ho and then Dr. Grimmett.

DR. HO: Keeping in mind what we are trying to do here, risk/benefit presbyopia versus loss of vision from a cataract, I would almost look at these numbers and say, you know, ratchet me down one log unit down the board and I would almost find that acceptable I think.

DR. GRIMMETT: I agree with Dr. Stark that the cumulative macular edema at three percent seems high. I think that is too high to be acceptable in clear lens extraction.

As I mentioned earlier, the cumulative hyphema rate--I was astounded to see that it is listed at 2.2 percent, quite frankly, because just thinking about my practice I just don't see hyphemas after cataract surgery certainly with modern phaco. That is why I was wondering if that was driven by old extra-cap or some other type of surgery. Does anybody else here see hyphemas after cataract surgery? So, I think for that rate to be an acceptable rate and just let it ride, I think

that should be exceedingly low, hyphema after clear lens extraction. I can't remember one in ten years.

DR. STARK: And it will be because probably many of these were limbic incisions, scleral incisions and that is why there was a little circulating hyphema. But now, with clear corneal incisions it would be less than one percent.

DR. WEISS: Dr. Eydelman, you were saying this was from the '80s to the early '90s, this grid?

MR. CALOGERO: '87 to '96.

DR. WEISS: We do have something more recent than this or no?

DR. EYDELMAN: We have a draft of something that is more recent but it hasn't been vetted.

DR. WEISS: Do you need more from us on this? Dr. Rosenthal?

DR. ROSENTHAL: This, to me, is one of the bigger issues. You are subjecting patients to surgery with a cataract. These are the rates which have become acceptable to get a new lens on the market. Now, are you going to ratchet them all

down by a factor of ten or a factor of one-third? What is going to be acceptable? I can't imagine--I may be stupid but I can't imagine if you operated on patients for a refractive exchange that you are still not going to get a percentage of complications. They are not going to come out complication-free.

DR. WEISS: Right. Dr. Bressler?

DR. BRESSLER: I am going to echo what Allen said, and that is that when you already have good vision and a clear lens, having macular edema at the level of 0.3 percent might be the most that the subject could possibly comprehend and we were willing to accept a retinal detachment rate of that. I am somewhat comfortable accepting that as the macular edema rate that we want to be able to identify.

DR. WEISS: So, you would like the macular edema rate for three years to be what? This is the one-year rate for cataracts. What would you like for clear lens extraction?

DR. BRESSLER: I am still okay with 0.3 percent because in that case, again, it is going to happen almost all in the first year and you are not going to have people who then develop it additively

in the second or third year.

DR. WEISS: So, at least we have a comment on one of them of a 0.3 percent on macular edema. We are going to have Dr. Grimmett and then Malvina.

DR. EYDELMAN: Perhaps I can make it a little simpler. If we are talking about a three-year study for 300 subjects, or so, the maximum detectable rate for cumulative adverse events would be 0.3. So, perhaps we could ask do you feel that a rate of higher than 0.3 would be acceptable because we can't really detect with any precision anything below 0.3 percent?

DR. WEISS: So, what you are saying is for any of these categories, would we want to be less stringent than we are for the cataracts? Would we want a higher rate than what is being reported for cataracts? Did I misunderstand?

DR. EYDELMAN: No.

MR. CALOGERO: These are the mean rates here. We worked the statistics off these rates. If you have a pupillary block of, say, 0.1 percent that is the mean rate. This is a historical grid. Your study fails at one percent. So, your minimal detectable difference then would be 0.9. So, at the 0.1 you are failing at one percent. I ask what

Malvina is asking is what would you find acceptable. With a three-year study with 300 subjects it would be 0.33. That 0.33 would correspond to a much lower actual mean rate. In your actual study you could have a rate up to 0.33 and it would not be detectably different from the rate of 0.1.

DR. BRADLEY: I think we have basically got the idea that we are sample size limited and if we are specifying very low rates on a particular type of risk, lower than the rate which is driving the sample size, then we are not ever going to establish that rate. We understand that.

DR. EYDELMAN: Correct. Perhaps we can just concentrate on a few on the list which are above one percent or 0.8 and above and wee how those should be adjusted.

DR. WEISS: So, we are really only talking about hyphema and everybody agrees that rate is too high in macular edema.

DR. EYDELMAN: And secondary surgical intervention.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: So, the issue of macular edema is probably not correct because it is based

on prior literature, extracapsular procedures, etc. So, it is probably much lower to begin with because these are 1980 data through 19-something. So, phacoemulsification posterior chamber IOL has a much lower rate. You are asking us what rate is it or what should it be. Neil is an authority and has written a couple of papers. Where should it be in 2002?

DR. BRESSLER: It is still, unfortunately for the cataract surgeons, around one or two percent.

DR. WEISS: So, what rate would you like--

DR. EYDELMAN: Our unofficial revision showed 1.5 percent.

DR. WEISS: If the unofficial revision is 1.5 percent, would everyone feel comfortable leaving it at 1.5 percent for a clear lens extraction?

DR. BRESSLER: As an acceptable risk? Is that the question?

DR. STARK: You are talking about cumulative or persistent?

DR. EYDELMAN: Well, 1.5 was for cumulative at one year. You are absolutely right, now we are talking about a three-year study.

Perhaps a persistent macular edema of 0.5 in this grid--what should it be for clear lens extraction? Or, we can ask what is the cumulative macular edema over three years. They are two different questions.

DR. WEISS: Dr. Stark?

DR. STARK: I would say persistent at 0.5 at the end of three years would be the maximally acceptable rate.

DR. EYDELMAN: So, that high is acceptable?

DR. STARK: It can be lower.

DR. WEISS: Dr. Mathers has pointed out it is going to be that high so it would have to be acceptable because basically it is the same procedure and Dr. Grimmett is agreeing. Dr. Bressler, and then I would like to move on from that. Yes, Dr. Bressler?

DR. BRESSLER: My question is in reference with what Dr. Rosenthal said, and that was, you know, what are we going to accept? And, these are individual events again. Is there any sort of guide that is needed, required or recommended in terms of if you add up all the adverse events that could occur, because you have persistent edema,

plus retinal detachment, plus something or other?

DR. EYDELMAN: For IOLs we have not designed studies like that. We have criteria like that under LASIK studies but we have never done IOL studies in such a way.

DR. BRESSLER: For a patient who otherwise has normal vision except for their presbyopia, this is more analogous to LASIK than to the IOL so I would suggest you consider those.

DR. WEISS: I am in a hundred percent agreement with Dr. Bressler. I think where we are going to have to be moving is having a hybrid between cataract IOL and refractive surgery because really this is a medical procedure, whatever, that has been done for people who have lost best corrected vision but it is being done for refractive purpose. So, I think we have to have grids more similar to those we have for refractive surgery patients.

DR. EYDELMAN: So, if I can challenge you further then, can you recommend a cumulative acceptable adverse event rate for a three-year study?

DR. BRESSLER: What was it in your refractive surgery ones?

DR. EYDELMAN: Those aren't three-year studies.

DR. BRESSLER: What was it? One year?

DR. WEISS: One-year study.

DR. BRESSLER: Better people than I thought about that for a long time--

DR. ROSENTHAL: Five percent--

DR. EYDELMAN: It was five percent but that included microkeratome so it was a combination.

DR. WEISS: So, we had a five percent adverse event for one year in LASIK.

DR. ROSENTHAL: Correct.

DR. WEISS: So, would anyone be willing to come up with what percent should be for visually significant adverse events or what type of adverse events would you suggest?

DR. BRESSLER: Well, it would be hybrid. It would mainly be driven by things that affect visual acuity.

DR. WEISS: Should there be a similar one year for this?

DR. BRESSLER: Cumulative, yes, and that seems a little high to me for this but I think that is because we are talking about more visually

significant events than what you suggested from the LASIK.

DR. ROSENTHAL: Correct.

DR. STARK: And also for refractive, Neil, you can't have more than a certain vision loss, and I can't remember what that is, but that should be tied in with it. Vision-threatening complications are what we want to get.

DR. WEISS: We don't have the refractive table in front of us but I am hearing sentiment, and I certainly have that sentiment, that this study should be basically looked at in addition in the same way that we looked at our refractive surgery studies because this is a refractive surgery indication, and Dr. Mathers seems to agree with that. Do you need anything else from us on this? Hyphema, did you need that from us? I think that should be a fairly trivial rate. Do you want to throw out a rate, Mike? Dr. Rosenthal?

DR. ROSENTHAL: You are talking about we have to compare this, if I am not mistaking you, to two guidances, one is the guidance related to the surgical procedure; the other is the guidance related to refractive surgical procedure. Is that right?

DR. WEISS: I think that is what was being suggested by Dr. Bressler, the reason being, as he points out, these people are coming in with normal best corrected and they want to know--

DR. ROSENTHAL: I understand.

DR. WEISS: --what their cumulative effect is. If that is fine with the agency, we are going to go to 5 C), do additional adverse events need to be collected? If so, what should their acceptable rates be? I think one additional one is just looking at it cumulatively, looking at it another way. Dr. Brown?

DR. BROWN: Loss of best corrected visual acuity.

DR. WEISS: So, loss of best corrected visual acuity.

DR. ROSENTHAL: That is part of refractive surgical guidance.

DR. BROWN: Okay.

DR. WEISS: If there are any other ones on the refractive surgical guidance that are not coming to mind, I think those would have to be considered by the agency as far as what would be relevant to this. Dr. Brucker?

DR. BRUCKER: I assume that corneal

decompensation, penetrating keratoplasty are automatically written in there.

DR. EYDELMAN: Yes.

DR. WEISS: Dr. Stark?

DR. STARK: One other thing, just to make sure that once a patient is entered into the study and they get to the operating room, if they have surgery and then they don't get an intraocular lens, that they are still continued in. So, there are going to be some situations where the patient doesn't get the implant after the incisions are made so we are going to have to come up with what is an acceptable rate of that too. Vitreous loss for example, you don't want to lose that patient from the study and say, well, that didn't happen; that wasn't part of it.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: Actually, that comes into the definition of enrolled and once the surgical procedure begins that patient is considered enrolled and, therefore, any adverse events get captured regardless of whether the device was implanted or not.

DR. WEISS: Dr. Stark?

DR. STARK: You know, in the original IOL

studies we didn't have capsule rupture or vitreous loss because we assumed there would be no lens implants, and there were. So, you want to make sure that if the capsule is ruptured or there are surgical complications that these be recorded, especially if the lens is implanted with a vitrectomy. We would want to be able to capture that information.

DR. EYDELMAN: That is actually all on the current ISO forms.

DR. BROWN: Can I just add one item?

DR. WEISS: Dr. Brown?

DR. BROWN: This may be putting a hypothesis out before we really have strong data but one issue is in replacing the crystalline lens in young patients who are going to have to have this for many years, and does the lack of the properties of the crystalline lens promote the progression of retinal draws in patients who may likely develop AMD later in life? So, you know, it might be worthwhile in the post-marketing study to have a fundus exam and five years may not be long enough but it certainly would be worth at least documenting the fundus appearance for long-term adverse effect.

DR. ROSENTHAL: Is that accepted, Dr. Brown?

DR. BROWN: No, that is what I am saying, it is a hypothesis before we really have data for that. It is just something to think about.

DR. WEISS: Question 6, FDA believes that all multifocal IOLs' safety and efficacy profile will have to be established in a cataractous population prior to initiation of a clinical trial in a non-cataractous population. Multifocal IOL performance cataractous population will, therefore, be known for all tests and sub-studies outlined in ANSI draft standard for MIOLs. Which sub-studies do you recommend for inclusion in the clear lens extraction protocol for evaluation of performance in this non-cataractous population?

One thing that I am going to ask--this is sort of similar to the refractive surgery population--I would like to know visual acuity postop in terms of what percentage of people are wearing glasses. I don't know if that would fit in here or fit somewhere else but is that going to be a criterion in these studies? Because if 40 percent or 50 percent are still wearing glasses, obviously, it didn't have the impact that one would

hope.

DR. EYDELMAN: That would go under subject survey. Under the study those are all the evaluations done on all subjects.

DR. WEISS: I see.

DR. EYDELMAN: So, we are moving to the sub-studies. That implies that the subject survey would be repeated.

DR. WEISS: So, that would be under F), "others" in terms of the--

DR. EYDELMAN: No, it would not be a sub-study. It would be in the study.

DR. WEISS: It would be in the study as a subject study. Dr. Brucker?

DR. BRUCKER: Can I ask two questions? One, why do you make the assumption that you make without having any data to back it up? Second, if this study shows that there is no increased complication rate, why can't multifocal IOLs be judged on their own merit later on down the line without having to be in cataractous patients?

DR. WEISS: What assumption are they making, just for the first one?

DR. BRUCKER: If you can back up on the right side? The FDA believes that all multifocal

safety and efficacy programs will be established in cataractous patients. And, I am asking why are you making the assumption--because it says "we believe that..." and I am asking you if this trial now shows that there is no difference and there are no complication rates that are not predicted, etc., etc., etc. why should you do that?

DR. EYDELMAN: Generally, when we evaluate a brand-new device we start out with placing it in the population where the safety and risk benefit are different. In other words, As we try to place it in a subject that will benefit the most and have the least risk.

DR. BRUCKER: So, if this trial--I am playing devil's advocate--if this trial shows that there is no increased risk and the patients are benefiting, then anybody who submits an application for an intraocular multifocal lens in the future should be able to put it in either population.

DR. EYDELMAN: Well, we don't have a trial yet so today we are discussing the status as of today.

DR. BRUCKER: You put that slide up; I didn't.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: These are Class 3 devices so that any time a new one comes on the market it has to be studied. You can't find a substantial equivalent to an existing IOL.

DR. BRUCKER: Right.

DR. ROSENTHAL: You have to study it.

DR. BRUCKER: Right, so I am saying--

DR. ROSENTHAL: And if you are going to study it, I think the agency has taken the tack that you should study it in a population that has cataracts first because we have well-established guidelines for what is required for an IOL to get through the process. Now, if a company wants to come here and study it in a non-cataractous population, they are welcome to do so but we can't allow them to put it on the market for both populations until they have certainly studied it for one, and actually because the indication is totally separate. As you can tell, it has taken up a day's worth of discussion on the issues related to this one. We would not allow them to get the second indication without a study. Have I made that clear in my unclear way?

DR. BRUCKER: That is a different explanation. It is an explanation of why it is

believed.

DR. WEISS: So, we are fine on that. We are going to go on to Dr. Bradley and what I am going to ask is, anyone who decides to answer this one, if you can indicate whether you want any of those sub-studies or any other sub-studies.

DR. BRADLEY: I think Dr. Brucker's comment relates to the issue of the risk associated with lens extraction surgery and is quite correct I think. There would be no need to employ a cataractous group. I think the issue at hand though is with each novel, potentially multifocal lens which can have its own specific risk and efficacy problems, because of that unknown presumably the FDA has chosen to employ a group for which the risk/benefit ratio is different. It is not the surgery.

DR. WEISS: Thank you, Arthur. Now, for the second part of your answer, do you have any comments on that, succinctly put?

DR. BRADLEY: Could you give me a minute?

DR. WEISS: I will give you a moment. Dr. Brown and then Dr. Mathers.

DR. BROWN: For efficacy I would like to see a reading speed under functional performance to

see that you have actually improved that.

DR. WEISS: Is there such a study that is done in terms of reading speed?

DR. BROWN: There are validated tests that use standardized text format, placement, lighting.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: And the reason we are asking this, as has been alluded to before, you are taking patients with, hopefully, 20/20 vision clear lenses and you are taking them out and putting in multifocal lenses. Do you want to see is there a drop in contrast sensitivity? I think obviously fundus visualization we would include in all of them just because it is good medicine. But, you know, it is not taking the cataractous lens where we don't require--well, we require sometimes these sub-studies but you are taking someone who has a clear lens or a peripheral cataract, or something, and are there changes that occur that you want to inform the patient about that may be of importance to both them and to the doctor?

DR. WEISS: Dr. Brown, would you want to exclude any of these? Would you want to include all of them? I think most of us would say fundus visualization. You need contrast sensitivity, I

would think. Your well-taken point of at least one aspect of looking at functional performance. Endothelial cell evaluation has come up before so I think there would be agreement on that. For defocus curves I would defer to everyone else on the panel. Is there anything here that you wouldn't want or anything in additional that you would want? You would go along with that? Dr. Mathers, then Dr. Ho, then Dr. Brucker.

DR. MATHERS: I would like to see glare testing and I would also like to have recorded symptoms of halos and symptoms of glare, not glare testing.

DR. WEISS: So, I think we are going to need a survey which has the subjective symptoms of those phenomena that we know you can get with these sort of IOLs, in additional to the refractive type of questions that you would ask as far as what sort of activities can you do without your glasses. Dr. Ho?

DR. HO: Ralph, can you just explain a little bit more? Are you saying that fundus visualization is just perfunctorily put on any IOL follow-up? You may not need to do a study. It is harder to see the fundus through multifocal IOLs.

DR. ROSENTHAL: Well, we know that.

DR. HO: Okay.

DR. ROSENTHAL: But we have to know whether it is so hard that if they do get a problem in the back of the eye it won't be able to be dealt with.

DR. WEISS: That is why we have retina specialists. Dr. Maguire?

DR. MAGUIRE: I don't if anybody has given any thought to this, but it is not just seeing in the back of the eye; it is doing laser treatments to the peripheral retina when they develop holes and retinal detachments and everything else later on, and also visualization. This is a real mixed group here. I mean, we have an Array lens which has degraded optics to get increased depth of field. We have the newer lens that has a very small diameter and you are going to have to try and get your lens around that to get out in the periphery. I don't know if it is possible or whether it is within agency boundaries but I would like to see some good studies on how laser energy is delivered to the peripheral retina on these different types of intraocular lenses because that is a real public health issue too.

The other thing is for defocus curves in lenses that suggest that they create some portion of the presbyopic correction through accommodation, I think a Hartman Schack analysis at a place like Dr. Williams' place in Rochester, New York or something like that to actually prove that they are getting their effect from accommodation and not from increased depth of field.

DR. WEISS: We don't really have to have an improved mechanism; we just have to have improved results.

MR. CALOGERO: Can I clarify a little bit here? All this testing here would already have been performed on, say, a multifocal lens in the cataract population. The question is now you are simply changing the population. You have a younger population that didn't have a cataract. Is there any expectation that the results in any of these tests may be different simply because you are putting it in this new population? We don't want to repeat all these tests if they are not necessary.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: Functional performance certainly because you are taking patients with

cataract initially who already have decreased optical function. Now you are taking people that are normal and exposing them to lenses that sometimes have degraded optical performance to increase depth of field. Obviously, they may get a different response than the cataractous group.

MR. CALOGERO: We have already had the results from the functional test--

DR. WEISS: For the cataractous population. I think Dr. Maguire knows that.

DR. MAGUIRE: But you are starting from a different baseline.

DR. WEISS: I have heard the panel members sort of agree that at least functional performance should be repeated in this population. From what I understood that Ralph just said, fundus visualization is going to be repeated whether we say it should or not. Is that correct? That is going to be part of the protocol whether or not we recommend it? Yes, you can elucidate.

DR. EYDELMAN: If I can just clarify something, you mentioned about functional. You wanted an addition of reading speed and that is a separate issue and we all agree. But currently the testing that is recommended under functional is

driving simulation. So, what we are asking is if functional needs to be performed, then your recommendation is that the company does a second driving simulation to show the difference between preop and postop in this new population. That is specifically 6 A).

DR. WEISS: I personally would want that because these people came with presumably excellent best corrected visual acuity at distance preop and if we found that their functional for the driving simulation had decreased, that is something patients would want to know. With the cataractous population presumably it would improve. But here the best corrected at distance may not improve; it could get worse. Does anyone disagree with that? Dr. Bradley?

DR. BRADLEY: I am not disagreeing.

DR. WEISS: Okay. So, I think we all agree that functional performance, we want what is already being performed to be repeated in this population in additional to near vision functional performance, which was suggested to be reading speed.

DR. EYDELMAN: A second clarification, glare testing is part of contrast sensitivity.

DR. WEISS: Then do people feel that contrast sensitivity should get repeated in this population? I see nods and I see nods fairly uniformly so we want contrast sensitivity repeated again in this population.

Defocus curves, do people want that repeated in this population? I see definite no responses on that one. So, we don't have a lot of strong interest one way or another on defocus curves.

Fundus visualization, do people want that repeated in this population? One no and a question. Dr. Grimmett?

DR. GRIMMETT: Was that helpful in the original evaluation of some of these lenses in the cataractous population? Did that help you one way or the other?

DR. EYDELMAN: Well, we have only had one MIOL approved so far, and what was required of that MIOL is different than what is recommended currently in the ANSI. We had a specific small sub-study where they did more than just look but there was a lot of discussion on the ANSI and that is the current recommendation. Since this is now a population after clear lens extraction that is

going to be around longer that might need laser treatment, that might have RD, do we need something more specific than a general questionnaire for this population that will clarify visualization of the retina? That is where this is going, or hoping to go.

DR. WEISS: Dr. Ho?

DR. HO: There is no reason to believe that there is a difference between the clear lens group and the cataractous group, in my opinion. If you want to get to the next level, as Leo suggests, or maybe a couple of levels up in terms of doing studies of energy and things like that, I think that is a separate issue. I would argue those are interesting studies. I think they would be worthwhile studies but I am not sure that--as you have described it, we know that it is more difficult to see through them or to operate through them or to laser through them.

DR. WEISS: What about the question about vitreous adhesions in the younger population that are going to be the subjects here? Do any of the retina folks have concerns about that as far as fundus visualization? I see no. Dr. Brown and then Dr. Bradley.

DR. BROWN: In that original study did you look at the peripheral retina? Was that part of the fundus visualization or was it just macular? Do you know?

DR. EYDELMAN: It was the whole retina.

DR. BROWN: And it was graded on some sort of 1-4 kind of thing?

DR. EYDELMAN: I don't remember how much of it was discussed in the open public hearing.

DR. WEISS: Dr. Bradley and then Dr. Brucker.

DR. BRADLEY: Well, we finally go on to the issue of effectiveness of these lenses after talking about risk all day. I have several comments on that. First off, we are all aware that there are three ways you can provide near vision for presbyopia, in this case a lens that is inserted into the eye. One is that you can make them a little bit myopic. One is that you can aberrate the lens and give them increased depth of focus. Finally, you can actually have a lens that can change power, that is a truly accommodative lens. All three have been used. I think at one level, whatever study design is done, would be able to discriminate between those three techniques and

that is very important.

The one we are specifically talking about today is the multifocal because I think that is the first batch of lenses that are going to come through the FDA. The accommodative ones, we will see plenty of those soon I think. These multifocal lenses come with their own concern, that is, they provide improved near vision at the cost of degraded distance vision. So, it is essential that distance vision be monitored very carefully with these lenses.

It is very important to ensure that the issue of pupil size is examined in this patient population because in a highly aberrated eye the aberrations will have more and more impact as the pupil dilates. This, obviously, is particularly true for these patients at night. Therefore, for the issue of safety and visual function the most important issue to monitor is night vision at distance; is that compromised in these patients? That is the most critical situation.

The question was do we measure glare testing? That is one thought. Do we do night vision driving? First off, glare testing is a very poor technique for assessing night vision problems,

as you already know. You turn on the glare source, the pupil constricts, etc., etc. So, that doesn't work very well. Night vision driving simulations, the average night vision driving simulator is a very poor simulator of night vision. The reason for it is that if it is entirely computer based, the computer can generate about 100 to 1 range of intensities. The entire reason that you have night vision problems when you drive is that you are talking about millions to 1 intensity range in the environment, that is, dark road, very bright headlights. The typical night vision driving simulator cannot simulate that and that should be known and built into any study design. Try and get one that can accurately simulate the intensity range that is going to exist at night. So, I am very concerned about the large pupil, the night vision problem at distance.

We move on to the issue of near vision. How do you assess near vision? There really aren't any standard ways that are particularly good, in my opinion. I do like the idea of having a near reading test. In the end, that is what the patients want. They are all presbyopic, coming to their clinician because they can't read anymore.

So, I like the idea--whoever presented it--of doing a reading test. It is my personal experience, now becoming a presbyope--that the particular near test that is so critical is reading a low contrast text. Any parents who have children who play video cards will know all about this. It is 4-point type; it is very low contrast; and you simply can't read it unless you are well refracted at near. Likewise, patients trying to read prescription bottles where they have poor print.

Finally, I think the issue of near vision can be evaluated in a survey with assessment of spectacle use. I think a series of questions on that topic will help. Again, spectacle use under different circumstances--do you need your spectacles in a restaurant at night, dim light, trying to read the bill? That is when I need my reading glasses.

So, be aware that there are ways to assess near vision but they are not standard clinical tests, and I think those should be employed. Thank you.

DR. WEISS: Those are really excellent comments, Arthur, and I think your sort of directing these to what the issues with this

particular technology is going to be is a very, very important additional to this. Dr. Brucker?

DR. BRUCKER: Just a question, have fundus photographs ever been done as a sub-study?

DR. EYDELMAN: That was part of the original sub-study for the first MIOL but it is no longer recommended. So, if that is your recommendation that would be something additional.

DR. BRUCKER: As long as it has been done--

DR. EYDELMAN: Well, it was done for only one IOL. It is not going to be done for other MIOLs that are coming along.

DR. BRUCKER: That would be a mistake, but if this IOL has been reviewed then it doesn't need to be done.

DR. WEISS: Well, you can request that if the IOL has not had this done that it should be done. You could include that.

DR. BRUCKER: We have an aging population, macular degeneration first and angiography laser treatment. It ought to be known whether you can do a photograph through one of these things.

DR. EYDELMAN: How many subjects do you feel you would need to assess that?

DR. BRUCKER: Half a dozen.

DR. EYDELMAN: Originally we had a sub-study of ten.

DR. BRESSLER: You mean five that had it and five comparison?

DR. EYDELMAN: I think it was ten and ten.

DR. BRESSLER: That is fine.

DR. BRUCKER: That is fine.

DR. BRESSLER: You can tell very quickly I think.

DR. WEISS: So, what I hear is that we don't need fundus visualization because it has been done already but it would be helpful to know whether you can photograph these people. Dr. Brown?

DR. BROWN: But I do think that as each new technology comes out that that be replicated for visualization also. For the periphery is what I am particularly just curious about, whether they are going to get to the edge of this lens? Does it distort the view so much that you can't see?

DR. WEISS: Would you be satisfied though with, let's say, ten eyes or ten patients as well? So, it is a very, very small subset to look at the periphery and do photos to see if that would be

impaired by the IOL? Does that seem satisfactory to the retina folk among us?

Endothelial cell evaluation, is that something that we want to repeat in this group if it has been done in the cataractous population, that is fine?

DR. BRUCKER: I would say that if the flow of liquids, flow of aqueous and the dynamics in the eye is not thought to be detrimental or changed by the irregularity of the surface of the lens, then you don't have to do endothelial cell counts. But if you have a lens that shimmies and has a particular configuration that the physicists think may be causing current change in the eye, then you should look at it because you may lose endothelial cell count.

DR. EYDELMAN: I just want to clarify, there are no endothelial cell sub-studies in the regular MIOL. That was not on the list; that was an additional criteria.

DR. WEISS: This one was not performed before--

DR. EYDELMAN: Correct.

DR. WEISS: --so if you want it done, it would have to be done in this population.

DR. EYDELMAN: Correct.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: I would be in favor of an endothelial cell sub-study even if the data exist in the cataractous population. You are looking at a different age range and you may have different endothelial dynamics, endothelial cell layers more robust in the young. You may find different things depending on the age range that you look at. I would be in favor of having an endothelial cell sub-study.

DR. WEISS: We are going to have one more comment by Dr. Smith. Then, if we are okay with the agency, we will go on to the next. Dr. Smith?

DR. SMITH: I would just echo Dr. Grimmett's comments and say it is very important to add that.

DR. WEISS: I would want that done as well in the post-market study.

DR. EYDELMAN: Wait a second, are you saying you want it in the pre- and post-market study? Because from what I understood in the discussion before, the post-market is going to be very large and it is going to be a yes or no.

DR. WEISS: Actually, I will withdraw what

I just said. Any other studies that we want aside from the survey for which Dr. Bradley had mentioned a bunch of things?

DR. STARK: Did we decide that vitreous examination and documentation was too difficult to do?

DR. WEISS: We decided that there would be five or ten patients that would have periphery of the retina as well as photographs done.

DR. STARK: I am talking about documentation of the status of the vitreous and vitreous--

DR. WEISS: I don't think that was going to get done. Dr. Brucker?

DR. BRUCKER: I don't think it is very practical. OCT would be great but only within several millimeters of that surface, it is probably not worthwhile.

DR. WEISS: So, that won't get done. If agency is fine, we will go on to question 7. The only current performance efficacy endpoint for aphakic posterior chamber IOLs, FDA grid, is postoperative best corrected vision of 20/40 or better in 92.5 percent of the subjects. Is this applicable to non-cataractous eyes undergoing clear

lens extraction for the correction of presbyopia? Dr. McMahon?

DR. MCMAHON: No.

DR. BRESSLER: I agree.

DR. WEISS: Dr. Bressler agrees. So, I assume you want higher criteria. Do you want from us what the higher criteria are or is all you need to know that that is not going to be sufficient for this population?

DR. EYDELMAN: Well, you have decided to have an inclusion criteria of 20/20 so it is up to you whether you want to set an efficacy endpoint of maintaining BC of 20/20 post surgery or not.

DR. STARK: Don't we have criteria already for the refractory surgery protocols? It would seem to me like you would keep those same criteria and you would agree that a few may lose one or ten letters, or whatever, but after a while we should set a standard similar to the refractive surgery protocol.

DR. WEISS: I would agree with that.

DR. EYDELMAN: The only criteria we have in the refractive is for UCVA and predictability. We don't have criteria for BCVA and that would be okay.

DR. STARK: I thought we had loss of--

DR. WEISS: It is one or two lines--

DR. EYDELMAN: That is safety; that is not for efficacy.

DR. WEISS: I see.

DR. EYDELMAN: It is an efficacy endpoint.

DR. WEISS: But what is the percentage for the loss of two lines or more BCVA.

DR. ROSENTHAL: It is one percent.

DR. WEISS: One percent? Then we are talking about 99 percent. If they were all starting out 20/20, it would have been 20/30 or better. Is that correct if you translate it over to efficacy?

DR. EYDELMAN: If you want to keep it as safety and not introduce efficacy in terms of BCVA, that is fine. You don't have to create additional criteria; you can stick with--

DR. BRADLEY: Let's keep it as safety.

DR. WEISS: Dr. Stark?

DR. STARK: If you look at it in efficacy you have to take into consideration the magnification of the myopes and the minification of the hyperopes. But I think we should have it as an efficacy issue also.

DR. WEISS: I think we also need a best corrected visual acuity standard and the question is what number do people want to come up with. You know, this is being done for refractive reasons and we wouldn't want too many people losing vision. Dr. Bressler?

DR. BRESSLER: I just want to confirm what people are agreeing to on the table. One, I do think it should be done for safety because the efficacy is going to be all the wonderful suggestions that Dr. Bradley has brought up. I just want to confirm that we are discussing that it is going to be a change in letters of ten or more, for example, because if you start at 20/12 as some of these people may, then if they go below 20/20 that is an adverse event.

DR. EYDELMAN: Right. As far as safety, we always talk about ten letters or two lines of BCVA loss.

DR. WEISS: Does the panel want to have efficacy including what your best corrected visual acuity is or not in this case? No? That was a no?

DR. WEISS: Dr. Brucker?

DR. BRUCKER: So, you are willing to take a 7.5 percent visual acuity loss of three lines--

DR. WEISS: No, I don't think anyone wants to use that. That is not going to be applicable. The question was is that applicable here and I think the consensus of the panel was that it is not applicable.

DR. BRADLEY: It is a safety issue, the issue of best corrected visual acuity, and always has been. Obviously this would be unacceptable for safety--

DR. WEISS: We are saying it is no good; we don't want it. We are just saying it has to do with the safety; it is not efficacy. We are going to be judging these efficacious in different modes. That is satisfactory to the agency and we will go on to B), are the predictability outcomes outlined in FDA's draft guidance for refractive implants applicable, 75 percent of eyes standard MRSE plus/minus 1.0 diopter, 50 percent with MRSE plus/minus 0.5 diopter and uncorrected vision, 85 percent with 20/40 or better. Is that applicable here?

DR. WEISS: Dr. Bradley?

DR. BRADLEY: A suggestion to FDA to perhaps update these data to the better of the new lenses that you have seen. These old standards may

be too lax.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: There aren't for lenses. This is for refractive.

DR. WEISS: But I think we have to add to that near vision criteria.

DR. EYDELMAN: That is C), 7 C).

DR. WEISS: Is this sufficient for IOLs for distance and for refractive, plus/minus 1.0? Did you want to say something?

MR. MCCARLEY: Well, the only comment is I was going to ask you what are your guidelines for cataract lenses on predictability and so forth? I know this is more and this is the LASIK and phakic lens guidelines. There aren't any for regular IOLs.

DR. EYDELMAN: No, that is why I said the only efficacy endpoint for IOLs is BCVA.

MR. MCCARLEY: Exactly, that is my point.

DR. EYDELMAN: That is the distinction I was trying to make.

DR. WEISS: I think this also will have to change if we are doing higher myopic levels than what we are talking about because if these are going to be used for beyond what the LASIK

guidelines are, you can't apply the same levels if we are doing a very high myope. I don't think we are just in terms of the criteria that are set forth here. Walter?

DR. STARK: We need to add also uncorrected visual acuity and whether or not there is a drop in that. If we are taking plano patients for presbyopia and they are 20/20 we need to look at what percent of them are no longer 20/20 uncorrected afterwards.

DR. WEISS: Is that efficacy or safety?

DR. EYDELMAN: Change in UCVA would be efficacy--

DR. STARK: It would be efficacy; they could be corrected with glasses.

DR. EYDELMAN: BCVA would be safety and UCVA is efficacy.

DR. ROSENTHAL: Excuse me, let me have some idea of what the panel thinks should be the percentage of patients who have uncorrected visual acuity of something/something or better. If you are taking 100 patients that are 20/25 and 20/20 and 20/15 what percent of those do you allow to drop down to 20/40?

DR. EYDELMAN: Actually, it is the same

thing only a little bit twisted because you are taking essentially patients, many of whom will be UCVA 20/20 preop but the only postop criteria is that UCVA of 20/40 is a success. We don't have any UCVA of 20/20 as a success, as a set endpoint. Ultimately you can have 75 percent of your subjects 20/20 UCVA preop and 85 with 20/40 but only 50 20/20 so the UCVA went down but it would still be considered a success.

DR. WEISS: The thing is really what the criteria for the final percentage that need to be UCVA 20/20 is very dependent on who you are entering into the study. If 100 percent of those are emmetropes, then you might want a 95 percent 20/20--

DR. EYDELMAN: That is one question.

DR. WEISS: --if they are all minus 12 you are not going to have the same expectation. So, what we are going to tell you is going to be totally dependent on whom you are entering into the study. We could have them for different categories and say, you know, between plus 2 to minus 2 we have this expectation of UCVA; above minus 10 we have this expectation of UCVA.

DR. ROSENTHAL: That is what we would

like.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I pass.

DR. WEISS: You pass? So, you would like from us somewhat of a grid, what we want the UCVA of 20/20 percentage to be dependent on the entry criteria of the patients?

DR. ROSENTHAL: Correct.

DR. BRESSLER: Adjusted for induced magnification of course.

DR. EYDELMAN: That actually comes into effect only at 15 diopters.

DR. WEISS: Does anyone want to give us--Walter, do you have any guidance as far as what you would want percentage UCVAs to be for various groups?

DR. STARK: I would have to think about it but it would depend on the starting point. You know, it is a safety/efficacy issue, where they started, but I would have to give it some thought. We could develop that for you, recommendations.

DR. WEISS: If we are dealing with low myopes, low hyperopes and emmetropes what would we be saying--yes?

DR. EYDELMAN: I am just trying to think

of a typical subject. Theoretically, they are going to have clear lens extraction because they don't want to wear glasses. If they still need to wear glasses for distance but don't need to wear them for near, would that be a typical subject? Even though it is correction of presbyopia, would somebody who needs glasses for distance and near be happy with wearing glasses only for distance but not near?

DR. WEISS: Dr. Brucker?

DR. BRUCKER: I think that this is an elective procedure for emmetropes or anybody with refractive errors and if you turned around and took a hyperope and made them a little bit more hyperopic, even though they didn't need reading glasses anymore, they would be really, really, really unhappy. So, I think that this number of 85 percent with 20/40 vision would be unacceptable.

DR. WEISS: What would you like the number to be?

DR. BRUCKER: Well, I think that you should be having an uncorrected visual acuity closer to the 20/20 and a percentage considerably higher. It should be a more predictable way of coming to a conclusion in these elective patients.

I don't do refractive surgery so I don't know what is the realistic expectation but I would be pushing 90 and 95 percent coming within 20/20 vision.

DR. WEISS: Dr. McMahon?

DR. MCMAHON: I wrote exactly the same thing and said 95 percent or greater equal to 20/25, 20/30 depending on the group entrance level. I think you need to be in that range. I don't know if it is realistic but--

DR. WEISS: So, we have Dr. Mathers, Dr. Bressler, Dr. Maguire and then Dr. Bradley.

DR. MATHERS: I think 95 percent should see 20/30 at least. That is certainly attainable. That is reasonable.

DR. WEISS: While we are going around, does anyone want to throw in their criteria for near vision because this is being done for presbyopes so if you are getting excellent uncorrected distance acuity vision but your near visual acuity isn't any good, then it sort of makes the whole thing pointless but I will ask the other people answering these questions to address that as well. Dr. Bressler?

DR. BRESSLER: I wonder if there is some way of turning it around, because of the example

you gave where the uncorrected visual acuity doesn't drop more than ten letters, for example, because it may be that someone is 20/20 with their glasses and they just want to get rid of their presbyopia, and they may be a success at near even though their distance still requires their glasses. I don't look at that as a problem, if that was 50 percent of the cohort, if they all solved what they were trying to do, that is, get rid of their presbyopia. If it is to correct both their presbyopia and their distance visual acuity, that is a different question and that is not what we are dealing with. So, I would propose to see if there is a way that it could be worded so that, again, it is a ten letter or more loss from their distant uncorrected visual acuity and their near uncorrected visual acuity.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: If you were doing surgery for correction of near vision, having an efficacy of a drop of ten letters of near vision--

DR. BRESSLER: I took it better for near.

DR. STARK: He meant a gain, I bet.

DR. ROSENTHAL: He meant uncorrected distance and best corrected near.

DR. BRESSLER: That is correct.

DR. WEISS: Dr. Mathers?

DR. MATHERS: It is a little more complicated because most of these people have a little bit of monovision as well, and what they are really interested in is a binocular distance vision that is acceptable and a reading vision that is acceptable. That is usually 20/25 distance and J3 binocular, but the individual eye doesn't really matter to the patient. So, that is the reality of what they are really trying to get at and we can have relatively softer terms per eye as long as they get there together.

DR. WEISS: Dr. Hilmantel, did you have a comment? DR. HILMANTEL: Yes, you may want to consider some kind of target like 90 percent or 95 percent getting both distance and near of a certain level like 20/30, both simultaneously.

DR. WEISS: I am in agreement with you because the near hasn't been addressed and the near is the only reason that they are having this done. Dr. McMahon and then Dr. Bradley.

DR. MCMAHON: I would float a new target of 75 percent greater than or equal to J3 and 50

percent greater or equal to either J1 or J2, I am not sure which is the best there. I just think establishing a level for J3 is not good enough.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: It is worth considering that unlike the refractive surgeries that we have been looking at, the corneal ablative surgery, as you approach zero correction you are ablating this material, you introduce less error. In this particular surgery the error doesn't approach zero as the refractive error approaches zero. Add to that that we are talking about multifocal lenses, which are highly aberrated lenses, which must degrade vision to some degree, and you have an error for an emmetrope; you have a multifocal lens for an emmetrope and it seems to me that the emmetropic example that has been thrown around here is that they are all likely to have a significant decrease in their distance visual acuity and that is just the reality of this particular procedure.

A second point relating to near vision, I think that standard clinical tests, high contrast acuity, are likely to underestimate the problems experienced by patients at near, particularly with multifocal lenses and that is why I suggested a

reading task, preferably a low contrast reading task and preferably one in dim lighting would allow you to evaluate the actual near vision problems encountered by these patients.

DR. WEISS: I want to get back to the efficacy criteria that we are trying to skirt about here. We have a distance uncorrected visual acuity and we have a near uncorrected visual acuity. The distance uncorrected visual acuity, the numbers that I have heard right now sort of thrown out are 90 percent, 95 percent in the 20/25 to 20/30 range. I just want to know if there is some consensus on that distance visual acuity. Dr. Bradley?

DR. BRADLEY: Not sure.

DR. WEISS: Can we come up with a number for the agency as far as what we would consider efficacy for distance uncorrected visual acuity?

DR. BRADLEY: I think 100 percent better than 20/40.

DR. WEISS: A hundred percent better than 20/40. I personally would also like a higher level--it could be a lower percentage but a higher level of visual acuity and at least report the percentage, whether it is 20/25 or 20/30, or whatever. If 100 percent of people were 20/40 and

5 percent of people were 20/30 or better, I don't think any of us would consider this procedure efficacious. You are not that comfortable with it at 90 percent, 95 percent, 20/25, 20/30?

DR. BRADLEY: I think I would defer to the clinicians in the room dealing with patients. You have a sense of what they demand. I mean, the reason I think of 20/40 is that you need that to drive, and to take somebody who sees perfectly well with their spectacles and can drive, and then you give then a procedure to improve their refractive status and they can't drive is obviously a failure. That is one criterion I can be comfortable with.

DR. WEISS: Bill, you had suggested the 20/25, 20/30, 90 percent, 95 percent. Are you comfortable with that still?

DR. MATHERS: Yes, because I think that for driving you usually use both eyes. It is too stringent to say that 100 percent are going to be this because if you are coming from a plus 6 you might think your vision is a lot better even if that particular eye didn't quite get to 20/40 uncorrected and you are still going to be better off. So, 98 would be okay but I think 100 is too much.

DR. BRADLEY: You say 100 is too much but if you told the patients, by the way, 2/100 of your patients are no longer going to be able to drive after this procedure, nobody will have the procedure.

DR. WEISS: The agency wants to comment. After you comment I am going to ask you do you have enough--I know you don't have an answer from us but do you have enough information from us on this particular one because we are running behind? Yes?

DR. BLUSTEIN: Yes, 20/40 is just for an unrestricted driver's license. You can still drive with worse than 20/40.

DR. WEISS: Malvina, do you have enough information from us on this one? Enough information being established, the additional performance efficacy endpoints I think have already been discussed in terms of low contrast reading and maybe better driving function tests. If the agency is fine with that, we will go on with number 8, how do you recommend we evaluate patient's quality of life issue? I think a survey was mentioned. Does anyone have any additional ones? Dr. Eydelman?

DR. EYDELMAN: The question was specific to whether you can recommend a specific patient

questionnaire, not just do a patient questionnaire but can you go a step further and have any recommendations as to which one is appropriate?

DR. WEISS: There are three types of patient questionnaires on the screen, if anyone has any preferences as far as any of these go. Dr. Smith?

DR. SMITH: I am not going to express a preference for any outcome those specific questionnaires, however, I think it is important that refractive surgical type questions be in the questionnaire. All of those questionnaires don't include those types of questions. I think also the tasks that are being asked, some of them ask for specific tasks that are more specific for older individuals and the tasks that need to be asked about should certainly include driving and things that may be done by younger individuals.

DR. WEISS: And things that we have seen come before us already such as what percentage can read the newspaper without their glasses; what percent can read a restaurant menu, etc. without their glasses. Any other comments on this particular question? Dr. Rosenthal?

DR. ROSENTHAL: The two latter

questionnaires were done mainly for distance vision, and they were done early before near vision was considered a refractive surgical procedure. Does anyone have any information on near vision in the refractive surgical environment?

DR. BRADLEY: Certainly the impression I get from the silence around the table is that we are not familiar enough with these surveys but, clearly, you need to have questions that are going to assess near vision. You must have questions that are going to assess night vision and night driving. These are the obvious problems that these patients are going to experience. If these surveys do not include such questions you need to add them.

DR. ROSENTHAL: The surveys include a lot more about night driving and vision.

DR. WEISS: So, we need to add questions about reading. Dr. Smith?

DR. SMITH: Those questions then need to be validated. I mean, these are all validated questionnaires for distance.

DR. WEISS: Dr. Bressler?

DR. BRESSLER: I don't know about the NEI refractive but the NEI VFQ, visual function questionnaire, does include several questions to

get a subscale for near activities and it has been validated so that could perhaps be added to the ones you are looking at here.

DR. WEISS: The other thing is it may already include these but since the phenomena of the halos, star bursts and such seem to be a major side effect of these lenses, questions that address those also have to be in these surveys if they are not already. Dr. McMahon?

DR. MCMAHON: The one problem with using the VFQ for this is even though those questions exist, it was really designed for people who had poor vision so you would have substantial ceiling effects. That is where RQL actually was developed.

DR. WEISS: Well, I think you understand the sentiment, that this has to be more refractive surgery as opposed to diseased eye, and more set towards the younger as opposed to elderly individuals, with a lot of questions about visual quality and near vision. If there are no other comments on any--Dr. Bradley?

DR. BRADLEY: Finish your statement.

DR. WEISS: It was just if there are no other comments. I guess there are.

DR. BRADLEY: It doesn't really fit into

your questions but one issue I think that the FDA must address with these multifocal IOLs is how the patient is going to provide informed consent. I think this is not a trivial point with multifocal IOLs. How does the patient say yes, I agree to having multifocal optics when they have no idea what multifocal optics is; they don't understand the problems associated with multifocal vision? You cannot describe it to a patient and I wondered if the FDA had considered that. There are really two possibilities out there. Certainly one has been used. One is to provide the patient with simulated vision. I think Alcon did that with their Array lens. An alternative would be to have a sort of non-invasive version of multifocal optics provided to the patient, i.e., a contact lens. We saw that in our previous FDA panel meeting. That was for monovision. But, again, prior to the surgery can you provide the patient with some way so they can experience what multifocal optic vision is going to be like and, therefore, can provide informed consent? Because without the experience I am not sure they can actually provide informed consent.

DR. EYDELMAN: We actually tried to tackle

that problem and we recommended a couple of times multifocal contact trial before surgery. The problem is that not every MIOL design is paralleled exactly by the multifocal contacts. So, even though they will get a feel for what the multifocality might feel like, it won't be the same perception as when this is actually implanted. So, it is not a perfect solution.

DR. WEISS: You know, Arthur, there are things that we do to our patients every day that we can't really give them a full idea about.

DR. BRADLEY: Yes, but I am just a bit concerned. I think Dr. Maguire was alluding to this earlier, that a lot of these patients are not satisfied and want these lenses removed. I think that could have been avoided if they could have somehow seen what it was going to be like because this is a compromised vision situation, very clearly so.

DR. EYDELMAN: So, if your recommendation is for each sponsor to try to identify a multifocal contact lens which parallels the closest to their design, and to give the patients a trial--

DR. BRADLEY: Maybe a subgroup or something along those lines.

DR. EYDELMAN: Well, a subgroup won't solve your problem.

DR. WEISS: You know, Arthur, personally I think this is the problem you have in dealing with refractive surgery patients, to try to take out your bad candidates--which I assume the sponsor is going to want to do--up front because they are not going to want them filling out a survey saying they are dissatisfied when they can predict they were going to be dissatisfied no matter what happened. I think it is very hard to show the increased aberrations you have after LASIK. You can tell people about the quality of vision issues but it is hard to convey.

DR. BRADLEY: Yes, I agree and one last comment on that is Dr. Lane, who presented this morning, made a very clear statement. He said the clinicians want to provide, and I am quoting, true informed consent for this procedure. That is their goal, and he was sponsored by the IOL company so, clearly the IOL companies want this. The challenge is how do you do it.

DR. WEISS: That will be the last comment then. So, if the agency is fine with the answers to these questions, in the remaining few minutes we

have a second open public hearing session if there are any comments from industry. Mr. McCarley?

MR. MCCARLEY: I am just, again, sitting here as an industry person, I am trying to look at the companies that have a multifocal lens and want to have an accommodative IOL but also all of the others that simply have monofocal IOLs and I have looked at the literature also--correct me if I am wrong--most of the clear lens extractions up to now have been done with monofocal IOLs. So, we are looking forward. Why would we expect that to stop if they have other potential problems with multifocal lenses like potential degradation in optics and other issues? Why wouldn't I expect for a monofocal lens company to want to come in and try to treat presbyopia? In fact, today's title is clear lens extraction for the correction of presbyopia. Well, the correction of presbyopia, I believe, is done all the time, clear lens extraction just with the monovision. So, have we today addressed any of the issues for monofocal lenses or was today a multifocal lens discussion and an accommodative IOL discussion? Because that, to me at least so far, hasn't been the majority of clear lens extractions.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: The goal of today was to focus on multifocal and accommodative IOLs.

MR. MCCARLEY: So, would you then expect to have a separate meeting with separate issues for monofocal lenses that are currently available in cataract surgery, treating presbyopia with monofocal lenses?

DR. EYDELMAN: Only if we find that we can't take the panel comments to the next step. In other words, we are going to meet internally when the situation arises and decide if we have the answers. If we don't, we might call a meeting; if we do, we will not.

MR. MCCARLEY: I would expect that occasion to arise very quickly if you have some companies wanting to do monofocal lenses. You know, they are easier to do studies on compared to multifocal lenses.

DR. WEISS: Does the agency have any other comments? Do panel members have any other comments? If not, I am going to ask Sally for concluding comments.

DR. EYDELMAN: We just want to thank the panel. It was a very clear and very concise

discussion. We appreciate it.

DR. WEISS: I don't think it was as clear and concise as your presentation but thank you anyway.

MS. THORNTON: I just want to, again, thank the panel and echo Malvina's sentiments. It has been a long day and I think we have gotten a lot out of your hard work, and I appreciate your time and attention to this issue. Thank you.

DR. WEISS: The open meeting is adjourned.

[Whereupon, at 3:52 p.m., the proceedings were adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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